BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

searched 03/24/03

```
     FILE 'REGISTRY' ENTERED AT 17:21:34 ON 24 MAR 2003
L2             1 S CLIMBAZOLE/CN

     FILE 'EMBASE, BIOSIS, MEDLINE, CAPLUS, USPATFULL' ENTERED AT 17:22:26 ON
     24 MAR 2003
L3           237 S CLIMBAZOLE OR 38083-17-9/RN
L4       1249935 S SKIN OR DERMATOLOGICAL OR DERMAL
L5           111 S L3 AND L4
L6            54 S L5 AND PY<2000
L7            41 DUP REM L6 (13 DUPLICATES REMOVED)
L8        360195 S RETINOID OR RETINOL OR RETINYL ESTER OR RETINAL OR RETINOIC
A

=> s l7 and l8
L9             8 L7 AND L8

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10            8 DUP REM L9 (0 DUPLICATES REMOVED)

=> d l10 1-9 ab bib kwic

L10  ANSWER 1 OF 8  USPATFULL
AB     An amide of a hydroxy fatty acid amide in combination with either
       retinol or retinyl ester resulted in a
       synergistic repression in keratinocyte proliferation. The effects of
the
       retinol or retinyl esters in combination
       with hydroxy fatty acid amides were analogous to treatment with
       retinoic acid.
AN     1998:47979  USPATFULL
TI     Skin care compositions containing an amide of a hydroxy fatty
       acid and a retinoid
IN     Granger, Stewart Paton, Paramus, NJ, United States
       Rawlings, Anthony Vincent, Warrington, England
       Scott, Ian Richard, Allendale, NJ, United States
PA     Elizabeth Arden Co., Division of Conopco, Inc., Burlington House, NY,
       United States (U.S. corporation)
PI     US 5747051              19980505                              <--
AI     US 1996-721874          19960927 (8)
DT     Utility
FS     Granted
EXNAM  Primary Examiner: Venkat, Jyothsan
LREP   Mitelman, Rimma
CLMN   Number of Claims: 2
ECL    Exemplary Claim: 1
DRWN   No Drawings
LN.CNT 601
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI     Skin care compositions containing an amide of a hydroxy fatty
       acid and a retinoid
PI     US 5747051              19980505                              <--
AB     An amide of a hydroxy fatty acid amide in combination with either
       retinol or retinyl ester resulted in a
       synergistic repression in keratinocyte proliferation. The effects of
the
       retinol or retinyl esters in combination
       with hydroxy fatty acid amides were analogous to treatment with
       retinoic acid.
SUMM   The invention relates to skin care compositions containing an
```

amide of a hydroxy fatty acid and a **retinoid**, preferably **retinol** or **retinyl ester**.

SUMM **Retinol** (vitamin A) is an endogenous compound which occurs naturally in the human body and is essential for normal epithelial cell differentiation. Natural and synthetic vitamin A derivatives have been used extensively in the treatment of a variety of **skin** disorders and have been used as **skin** repair or renewal agents. **Retinoic acid** has been employed to treat a variety of **skin** conditions, e.g., acne, wrinkles, psoriasis, age spots and discoloration. See e.g., Vahlquist, A. et al., J. Invest. Dermatol., Vol. 94, Holland D. B. and Cunliffe, W. J. (1990), pp. 496-498; Ellis, C. N. et al., "Pharmacology of **Retinols** in **Skin**", Vasel, Karger, Vol. 3,(1989), pp. 249-252; Lowe, N. J. et al., "Pharmacology of **Retinols** in **Skin**", Vol. 3, (1989), pp. 240-248; PCT Patent Application No. WO 93/19743. It is believed that the use of **retinol** or esters of **retinol** would be preferred over **retinoic acid**. **Retinol** is an endogenous compound which occurs naturally in the human body and is essential for normal epithelial cell differentiation. **Retinol** is also considered much safer than **retinoic acid**. Esters of **retinol** hydrolyze in-vivo to produce **retinol**. **Retinol** and **retinyl esters** are considered safer than **retinoic acid**. Unfortunately, **retinol** and **retinyl esters** are less effective than **retinoic acid** at providing **skin** benefits. The present invention is based, in part, on the discovery that a combination of **retinol** or **retinyl esters** with amides of hydroxy fatty acids results in a synergistic inhibition in keratinocyte differentiation. The effects of hydroxy fatty acid amides combined with **retinol** or a **retinyl ester** were analogous to the effects of **retinoic acid**. Thus, a mixture of hydroxy fatty acid amides with **retinol** or **retinyl esters** mimics **retinoic acid** yet is easier and safer to use than **retinoic acid**.

SUMM . . . from about 0.025% to about 35% of a monocarboxylic fatty acid, ester, or amide. The compositions may also include a **retinoid**. Thornfeldt teaches that certain **retinoids**, namely isotretinoin, tretinoin, etretin (all of which are stereoforms of **retinoic acid**) and etretinate (an ester of trimethoxyphenyl **retinoic acid**) have proven efficacy against papulosquamous diseases. PCT Application WO/9325177 (Proctor and Gamble) discloses compositions for topical application to **skin** which contain a specific type of acyclic carboxamide coolant and may include **retinoids** such as **retinoic acid** and its derivatives (e.g., cis and trans). PCT application WO/9403156 (Rhone Poulenc) discloses a topical composition containing linoleic acid or a derivative as an active ingredient for treatment and prophylaxis of impure **skin** (e.g., **skin** affected by pimples, pustules, or comedones); the composition may also contain 0.025-0.1 wt. % of tretinoin. European Patent Application No.. . .

SUMM . . . (U.S. Pat. No. 5,216,148) disclose the use of specific complex carboxamides for treating and preventing neoplasms, dermatoses, and aging of **skin**. Van Scott et al. (U.S. Pat. No. 4,380,549) and Yu et al., (U.S. Pat. No. 4,363,815) disclose treatment of acne, dry, flaky, scaly **skin** with a hydroxyacid or the amide thereof. EP

0 582 458 discloses use of N,N-(1,4C alkyl) lauramide. EP 0 559 304 disclose the use of an amide containing a hydrocarbyl chain of at least 25 carbon atoms as a **skin** smoothening agent. Beauquey et al. (U.S. Pat. No. 5,308,551) disclose a **skin** washing and conditioning composition containing, among other ingredients, a 1-4 C alkanolamide of a 8-16 C fatty acid. Great Britain. . .

SUMM The art cited above does not disclose **skin** conditioning compositions based on synergistic combinations of hydroxy fatty acid amides with **retinol** or a **retinyl ester**.

None of the art cited above addresses the need for an effective alternative to **retinoic acid**.

SUMM The present invention includes, in part, a **skin** conditioning composition containing:

SUMM (a) from about 0.001% to about 10% of a **retinoid** selected from the group consisting of **retinol**, a **retinyl ester**, and **retinoic acid**;

SUMM The term "conditioning" as used herein means prevention and treatment of

dry **skin**, photodamaged **skin**, appearance of wrinkles, age spots, aged **skin**, acne, **skin** lightening, psoriasis, atopic dermatosis, controlling sebum excretion, increasing stratum corneum flexibility, and generally increasing the quality of **skin**. The composition may be used to improve **skin** desquamation and cellular proliferation.

SUMM The presence of a hydroxy fatty acid amide in the inventive product substantially improves the performance of **retinol** or a **retinyl ester**, i.e., a hydroxy fatty acid amide substantially increases the ability of **retinol** or a **retinyl ester** to affect cellular proliferation. A hydroxy fatty acid amide has no or little effect on improving **skin** benefit when used alone; a substantial increase in **skin** benefit is only realized when a hydroxy fatty acid amide is combined with **retinol** or a **retinyl ester**.

In short, the present invention is based, at least in part, on the discovery of synergistic interaction between **retinol** or a **retinyl ester** and a hydroxy fatty acid amide.

SUMM In a preferred embodiment of the invention, a **retinoid** is selected from the group consisting of **retinol** or a **retinyl ester**. According to the present invention, by virtue of including an effective amount of a hydroxy fatty acid amide into compositions containing **retinol** or a **retinyl ester**, the performance of the compositions is substantially improved. Alternatively, lower levels of **retinol** or a **retinyl ester** may be included in the composition containing a hydroxy fatty acid amide to equal the performance of a similar formulation. . .

SUMM The inventive compositions contain, as a first essential ingredient, a compound selected from the group consisting of **retinol** or a **retinyl ester**.

SUMM The term "**retinol**" includes the following isomers of **retinol**: all-trans-**retinol**, 13-cis-**retinol**, 11-cis-**retinol**, 9-cis-**retinol**, 3,4-didehydro-**retinol**. Preferred isomers are all-trans-**retinol**, 13-cis-**retinol**, 3,4-didehydro-**retinol**, 9-cis-**retinol**. Most preferred is all-trans-**retinol**, due to its wide commercial availability.

SUMM **Retinyl ester** is an ester of **retinol**. The term "**retinol**" has been defined above. **Retinyl esters** suitable for use in the present invention are C.sub.1 -C.sub.30 esters of **retinol**, preferably C.sub.2 -C.sub.20

esters, and most preferably C.sub.2, C.sub.3, and C.sub.16 esters because they are more commonly available. Examples of **retinyl esters** include but are not limited to: retinyl palmitate, retinyl formate, retinyl acetate, retinyl propionate, retinyl butyrate, retinyl valerate, retinyl isovalerate,. . .

SUMM . . . selected from retinyl palmitate, retinyl acetate and retinyl propionate, because these are the most commercially available and therefore the cheapest. **Retinyl ester** is also preferred due to its efficacy.

SUMM The **retinoid** is employed in the inventive composition in an amount of from about 0.001% to about 10%, preferably in an amount. . .

SUMM . . . for the active components in the composition, so as to facilitate their distribution when the composition is applied to the **skin**.

SUMM Optional **Skin** Benefit Materials and Cosmetic Adjuncts

SUMM . . . invention. Various types of active ingredients may be present in cosmetic compositions of the present invention. Actives are defined as **skin** or hair benefit agents other than emollients and other than ingredients that merely improve the physical characteristics of the composition.. . .

SUMM Yet another preferred optional ingredient is selected from azoles, e.g., **climbazole**, bifonazole, clotrimazole, ketoconazole, miconazole, econazole, itraconazole, fluconazole, terconazole, butoconazole, sulconazole, lionazole and mixtures thereof.

SUMM The composition according to the invention is intended primarily as a product for topical application to human **skin**, especially as an agent for conditioning and smoothening the **skin**, and preventing or reducing the appearance of wrinkled or aged **skin**.

SUMM . . . a small quantity of the composition, for example from 1 to 5 ml, is applied to exposed areas of the **skin**, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the **skin** using the hand or fingers or a suitable device.

SUMM The topical **skin** treatment composition of the invention can be formulated as a lotion, a fluid cream, a cream or a gel. The. . .

DETD The following specific examples further illustrate the invention, but the invention is not limited thereto. **Retinoids** were obtained from Sigma.

DETD **Retinoic acid** is more effective than **retinol** at altering keratinocyte differentiation state

DETD The effect on Transglutaminase levels normalized to DNA content of the cells after addition of **retinoic acid** and **retinol** was examined and the results are shown in Table 1.

DETD All concentrations of **retinoic acid** tested, i.e., 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M decreased keratinocyte differentiation over both the ethanol control and did so to a significantly greater extent than each of the corresponding 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M **retinol** treatments. The decrease in transglutaminase level was dose dependent for both **retinoic acid** and **retinol**. This is consistent with **retinoic acid** having a greater inhibitory effect on epithelial differentiation than **retinol**.

DETD Amides of hydroxy fatty acids and **retinol** act synergistically

to repress keratinocyte differentiation

DETD TABLE 2A

Effect of **Retinol** And C.sub.13 .beta.-Hydroxy Acid Amide On Keratinocyte TGase/DNA

	mean TGase/	p value vs.	p value vs	p value vs 10.sup.-6
(100%)				
2.5 .times. 10.sup.-8 M RA	1.05 .+-. 1.05 (6%)	0.001	0.001	-- 0.001
2.5 .times. 10.sup.-8 M **Retinol**	14.62 .+-. 2.99 (79%)	0.001	-- 0.001	0.001
10.sup.-8 M C13-.beta.-hydroxy-acid amide	18.53 .+-. 4.58	0.875	0.001	0.001 --
(101%)				
2.5 .times.. . .				

DETD 2.5.times.10.sup.-8 M **retinoic acid** was very effective at repressing keratinocyte TG1 levels (to 6%) of control level. 2.5.times.10.sup.-8 M **retinol** was less effective than **retinoic acid** (79%) and 10.sup.-8 M C13 .alpha.-hydroxy-acid amide had no inhibitory effect on the keratinocyte TG1 level when used alone. However 2.5.times.10.sup.-8 M **retinol** +10.sup.-8 M C13 .alpha.-hydroxy-acid amide repressed keratinocyte TG1 to 62% of control levels. C13 .alpha.-hydroxy-acid amide and **retinol** therefore act synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid**.

DETD TABLE 2B

Effect Of **Retinol** And Lactamide MEA On Keratinocyte Differentiation

	mean TGase/	p value vs	p value vs	p value vs vs 10.sup.-6
. . . -- 0.110				
			0.002	0.001
(100%)				
2.5 .times. 10.sup.-7 M RA				

46.71 .+-. 7.83 (73%)
0.002
0.030
-- 0.049
2.5 .times. 10.sup.-7 M **Retinol**
58.47 .+-. 6.25 (91%)
0.110
-- 0.030
0.054
10.sup.-6 M lactamide-MEA
55.22 .+-. 2.43 (86%)
0.001
0.054
0.049
--
2.5 .times. 10.sup.-7. . .

DETD 2.5.times.10.sup.-7 M **retinoic acid** was effective at repressing keratinocyte TG1 levels (to 73%) of control level. 2.5.times.10.sup.-7 M **retinol** and 10.sup.-6 M lactamide-DEA were less effective at inhibiting keratinocyte TG1 level when used alone. However 2.5.times.10.sup.-7 M **retinol** +10.sup.-6 M lactamide-DEA repressed keratinocyte TG1 to 72% of control levels. Lactamide-DEA and **retinol** therefore act synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid**.

DETD Examples 1 and 2 demonstrate that **retinoic acid**, in a dose dependent manner, decreased keratinocyte differentiation. In Examples 1 and 2, **retinoic acid** was used as positive control and reference compound against which the other compounds under analysis were compared. **Retinol** was completely ineffective at decreasing keratinocyte differentiation.

DETD The unexpected results of Examples 1 and 2, however, were that the effect of **retinol** on cultured keratinocytes can be enhanced to levels approaching those of **retinoic acid** by combining **retinol** or **retinyl ester** with an amide of hydroxy fatty acid --a compound which exerts little or no benefit on its own. The results documented above demonstrate that an amide of hydroxy fatty acid acts synergistically with **retinol** or **retinyl ester**, to decrease keratinocyte differentiation, mimicking the effect of **retinoic acid**
.

DETD This example illustrates a non-aqueous **skin** care composition incorporating the inventive combination. ##STR10##

CLM What is claimed is:
1. A **skin** conditioning composition comprising (a) from about 0.001% to about 10% of **retinol**; (b) from about 0.0001% to about 50% of an amide of a hydroxy fatty acid selected from the group consisting. . .
2. A method of treating a **skin** condition selected from the group consisting of dry **skin**, photodamaged **skin**, wrinkles, age spots, aged **skin**, acne, **skin** lightening, psoriasis and atopic dermatosis, the method comprising applying to the **skin** the composition of claim 1.

L10 ANSWER 2 OF 8 USPATFULL

AB A polycyclic triterpene carboxylic acid in combination with either **retinol** or **retinyl ester** resulted in a synergistic inhibition of keratinocyte differentiation. The effects of polycyclic triterpene carboxylic acids in combination with

retinol or **retinyl ester** were analogous to
the treatment with **retinoic acid**.

AN 1998:21904 USPATFULL

TI **Skin** care compositions containing a polycyclic triterpene carboxylic acid and a **retinoid**

IN Granger, Stewart Paton, Paramus, NJ, United States
Scott, Ian Richard, Allendale, NJ, United States

PA Chesebrough-Pond's USA Co., Division of Conopco, Inc., Greenwich, CT, United States (U.S. corporation)

PI US 5723139 19980303 <--

AI US 1996-721878 19960927 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Faulkner, D.

LREP Mitelman, Rimma

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 646

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Skin** care compositions containing a polycyclic triterpene carboxylic acid and a **retinoid**

PI US 5723139 19980303 <--

AB A polycyclic triterpene carboxylic acid in combination with either **retinol** or **retinyl ester** resulted in a synergistic inhibition of keratinocyte differentiation. The effects of polycyclic triterpene carboxylic acids in combination with **retinol** or **retinyl ester** were analogous to the treatment with **retinoic acid**.

SUMM The invention relates to **skin** care compositions containing a polycyclic triterpene carboxylic acid and a **retinoid**, preferably **retinol** or **retinyl ester**.

SUMM **Retinol** (vitamin A) is an endogenous compound which occurs naturally in the human body and is essential for normal epithelial cell differentiation. Natural and synthetic vitamin A derivatives have been used extensively in the treatment of a variety of **skin** disorders and have been used as **skin** repair or renewal agents. **Retinoic acid** has been employed to treat a variety of **skin** conditions, e.g., acne, wrinkles, psoriasis, age spots and discoloration. See e.g., Vahlquist, A. et al., J. Invest. Dermatol., Vol, 94, Holland D. B. and Cunliffe, W. J. (1990), pp. 496-498; Ellis, C. N. et al., "Pharmacology of **Retinols** in **Skin**", Vasel, Karger, Vol. 3, (1989), pp. 249-252; Lowe, N.J. et al., "Pharmacology of **Retinols** in **Skin**", Vol. 3, (1989), pp. 240-248; PCT Patent Application No. WO 93/19743. It is believed that the use of **retinol** or esters of **retinol** would be preferred over **retinoic acid**. **Retinol** is an endogenous compound which occurs naturally in the human body and is essential for normal epithelial cell differentiation. **Retinol** is also considered much safer than **retinoic acid**. Esters of **retinol** hydrolyze in-vivo to produce **retinol**. **Retinol** and **retinyl esters** are considered safer than **retinoic acid**. The present invention is based, in part, on the discovery that a combination of **retinol** or a **retinyl ester** with a polycyclic triterpene carboxylic acid (hereinafter "PTCA") results in a synergistic inhibition of keratinocyte differentiation. The effects of PTCA combined

with **retinol** or a **retinyl ester** were analogous to the effects of **retinoic acid**. Thus, a mixture of PTCA with **retinol** or **retinyl esters** mimics **retinoic acid** yet is easier and safer to use than **retinoic acid**.

SUMM The present invention includes, in part, a **skin** conditioning composition containing:

SUMM (a) from about 0.001% to about 10% of a **retinoid** selected from the group consisting of **retinol**, a **retinyl ester**, and mixtures thereof;

SUMM The term "conditioning" as used herein means prevention and treatment of dry **skin**, photodamaged **skin**, appearance of wrinkles, age spots, aged **skin**, acne, **skin** lightening psoriasis, atopic dermatosis, increasing stratum corneum flexibility, controlling sebum excretion and generally increasing the quality of **skin**. The composition may be used to improve **skin** desquamation and cellular proliferation.

SUMM The presence of PTCA in the inventive product substantially improves the performance of **retinol** or a **retinyl ester**, i.e., PTCA substantially increases the ability of **retinol** or a **retinyl ester** to affect cellular differentiation. PTCA has no or little effect on improving **skin** benefit when used alone; a substantial increase in **skin** benefit is only realized when PTCA is combined with **retinol** or a **retinyl ester**. In short, the present invention is based, at least in part, on the discovery of synergistic interaction between **retinol** or a **retinyl ester** and PTCA.

SUMM According to the present invention, by virtue of including an effective amount of PTCA into compositions containing **retinol** or a **retinyl ester**, the performance of the compositions is substantially improved. Alternatively, lower levels of **retinol** or a **retinyl ester** may be included in the composition containing PTCA to equal the performance of a similar formulation without the PTCA.

SUMM The inventive compositions contain, as a first essential ingredient, a compound selected from the group consisting of **retinol** or a **retinyl ester**.

SUMM The term "**retinol**" includes the following isomers of **retinol**: all-trans-**retinol**, 13-cis-**retinol**, 11-cis-**retinol**, 9-cis-**retinol**, 3,4-didehydro-**retinol**. Preferred isomers are all-trans-**retinol**, 13-cis-**retinol**, 3,4-didehydro-**retinol**, 9-cis-**retinol**. Most preferred is all-trans-**retinol**, due to its wide commercial availability.

SUMM **Retinyl ester** is an ester of **retinol**. The term "**retinol**" has been defined above. **Retinyl esters** suitable for use in the present invention are C.sub.1 -C.sub.30 esters of **retinol**, preferably C.sub.2 -C.sub.20 esters, and most preferably C.sub.2, C.sub.3, and C.sub.16 esters because they are more commonly available. Examples of **retinyl esters** include but are not limited to: retinyl palmirate, retinyl formate, retinyl acetate, retinyl propionate, retinyl butyrate, retinyl valerate, retinyl isovalerate,. . .

SUMM The **retinoid** is employed in the inventive composition in an amount of from about 0.001% to about 10%, preferably in an amount. .

SUMM . . . for the active components in the composition, so as to facilitate their distribution when the composition is applied to the

skin.

SUMM Optional **Skin** Benefit Materials and Cosmetic Adjuncts

SUMM . . . invention. Various types of active ingredients may be present in cosmetic compositions of the present invention. Actives are defined as **skin** or hair benefit agents other than emollients and other than ingredients that merely improve the physical characteristics of the composition.. . .

SUMM Yet another preferred optional ingredient is selected from azoles, e.g., **climbazole**, bifonazole, clotrimazole, ketoconazole, miconazole, econazole, itraconazole, fluconazole, terconazole, butoconazole, sulconazole, lionazole and mixtures thereof.

SUMM The composition according to the invention is intended primarily as a product for topical application to human **skin**, especially as an agent for conditioning and smoothening the **skin**, and preventing or reducing the appearance of wrinkled or aged **skin**.

SUMM . . . a small quantity of the composition, for example from 1 to 5 ml, is applied to exposed areas of the **skin**, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the **skin** using the hand or fingers or a suitable device.

SUMM The topical **skin** treatment composition of the invention can be formulated as a lotion, a fluid cream, a cream or a gel. The. . .

SUMM The following specific examples further illustrate the invention, but the invention is not limited thereto. **Retinoids** used in the examples were obtained from Sigma. Ursolic and oleanolic acids were obtained from Aldrich. Glycyrrhizic acid was obtained. . .

DETD **Retinoic acid** is more effective than **retinol** at altering keratinocyte differentiation state

DETD The effect on Transglutaminase levels normalized to DNA content of the cells after addition of **retinoic acid** and **retinol** was examined and the results are shown in Table 1.

DETD All concentrations of **retinoic acid** tested, i.e., 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M decreased keratinocyte differentiation over both the ethanol control and did so to a significantly greater extent than each of the corresponding 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M **retinol** treatments. The decrease in transglutaminase level was dose dependent for both **retinoic acid** and **retinol**. This is consistent with **retinoic acid** having a greater inhibitory effect on epithelial differentiation than **retinol**.

DETD Glycyrrhizic Acid and **Retinol** Synergistically Inhibit Keratinocyte Differentiation

DETD TABLE 2

Effect of **Retinol** and Glycyrrhizic Acid on Keratinocyte TGase/DNA

mean TGase/ value	p value vs	p value vs	p value vs 10.sup.-6
. . . .times. 10.sup.-9 M			
4.04 .+-. 1.23			
	0.001	0.001	
		--	0.001

RA (33%)
2.5 .times. 10.sup.-9 M
8.29 .+-. 2.11
0.001 -- 0.001
0.001

Retinol (68%)
10.sup.-6 M
11.98 .+-. 3.00
0.774 0.001
0.001
--

Glycyrrhixic
(99%)
acid
2.5 .times. 10.sup.-9 M
5.41 .+-. 1.15
0.001 0.001
0.001
0.001

ROH. . .
DETD 2.5.times.10.sup.-9 M **retinoic acid** was very effective at repressing keratinocyte TG1 levels (to 33%) of control level. 2.5.times.10.sup.-9 M **retinol** was less effective than **retinoic acid** and 10.sup.-6 M glycyrrhizic acid had no inhibitory effect on the keratinocyte TG1 level when used alone. However, 2.5.times.10.sup.-9 M **retinol**+10.sup.-6 M glycyrrhizic acid repressed keratinocyte TG1 to 45% of control levels. Glycyrrhizic acid and **retinol** therefore acted synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid.**
DETD Oleanolic Acid and **Retinol** Synergistically Inhibit Keratinocyte Differentiation
DETD TABLE 3

Effect of **Retinol** and Oleanolic Acid on Keratinocyte TGase/DNA

	p	p value	p value vs	p value vs
mean TGase/	value	vs	vs	10.sup.-6
. . . .times. 10.sup.-7 M				
9.95 .+-. 2.74				
	0.001	0.001		
			--	0.001
RA (44%)				
2.5 .times. 10.sup.-7 M				
18.27 .+-. 3.30				
	0.001	--	0.001	
				0.001
Retinol (81%)				
10.sup.-6 M				
20.95 .+-. 1.95				
	0.001	0.001		
			0.001	
				--
Oleanolic Acid				
(93%)				
2.5 .times. 10.sup.-7 M				
14.83 .+-. 3.90				
	0.001	0.001		

. . .

DETD 2.5.times.10.sup.-7 M **retinoic acid** was very effective at repressing keratinocyte TG1 levels (to 44%) of control level. 2.5.times.10.sup.-7 M **retinol** was less effective than **retinoic acid** and 10.sup.-6 M oleanolic acid had only a very slight inhibitory effect on the keratinocyte TG1 level when used alone. However, 2.5.times.10.sup.-7 M **retinol**+10.sup.-6 M oleanolic acid repressed keratinocyte TG1 to 66% of control levels. Oleanolic acid and **retinol** therefore act synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid**.

DETD In Examples 1-3, **retinoic acid** was used as positive control and reference compound against which the other compounds under analysis were compared. **Retinoic acid**, in a dose dependent manner increased thymidine incorporation and decreased transglutaminase I levels in **skin** keratinocytes. In other words **retinoic acid** decreased keratinocyte differentiation. **Retinol** was significantly less effective than **retinoic acid** at inhibiting keratinocyte differentiation.

DETD The unexpected result of this study however was that the effect of **retinol** on cultured keratinocytes can be enhanced to levels approaching those of **retinoic acid** by combining **retinol** with a PTCA. This effect was not only greater than the effect of either **retinol** or the PTCA itself but the two ingredients acted in synergy with each other to promote a **retinoic acid** response on the keratinocytes.

DETD The results in Examples 2 and 3 demonstrate that PTCA acts synergistically with **retinol** both to increase keratinocyte proliferation and decrease keratinocyte differentiation, mimicking the effect of **retinoic acid**.

DETD

	% w/w
Retinol	0.5
Fully hydrogenated coconut oil	3.9
Ursolic acid	5
Brij 92*	5
Bentone 38	0.5
MgSO.sub.4 7H.sub.2 O	0.3
Butylated hydroxy toluene	0.01
Perfume	qs
Water	to 100

. . .

DETD

	% w/w
Retinoic acid	0.15
Mineral oil	4
Oleanolic acid	1
Brij 56*	4
Alfol 16RD*	4
Triethanolamine	0.75
Butane-1,3-diol	3
Xanthan gum	0.3

Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

*Brij. . .

DETD

	% w/w
Retinol	0.15
Glycyrrhetinic acid	0.1
Ethanol	40
Antioxidant	0.1
Perfume	qs
Water	to 100

DETD

	% w/w
Retinol	0.01
Ursolic acid	0.1
Silicone oil 200 cts	7.5
Glycerylmonostearate	3
Cetosteryl alcohol	1.6
Polyoxyethylene-(20)-cetyl alcohol	1.4
Xanthan gum	0.5
Parsol 1789	1.5
Octyl methoxycinnate (PARSOL MCX)	7

Perfume. . .

DETD This example illustrates a non-aqueous **skin** care composition incorporating the inventive combination.

DETD

	% w/w
Retinoic acid	0.15
Oleanolic acid	1
Silicone gum SE-30.sup.1	10
Silicone fluid 345.sup.2	20
Silicone fluid 344.sup.3	55.79
Squalene	10
Linoleic acid	0.01
Cholesterol	0.03
2-hydroxy-n-octanoic acid	0.7
Vitamin E Iinoleate	

. . .

CLM What is claimed is:

1. A **skin** conditioning composition comprising (a) from about 0.001% to about 10% of a **retinoid** selected from the group consisting of **retinol**, a **retinyl ester** and mixtures thereof; (b) from about 0.0001% to about 50% of a polycyclic triterpene carboxylic acid selected from the group. . .

2. The composition of claim 1 wherein the **retinyl ester** is selected from the group consisting of retinyl

palmitate, retinyl acetate, retinyl propionate, retinyl linoleate and mixtures thereof.

3. The composition of claim 1 wherein ingredient (a) is **retinol**.

4. The composition of claim 1 wherein ingredient (a) is a **retinyl ester**.

5. A method of conditioning **skin** the method comprising applying topically to **skin** the composition of claim 1.

6. A method of treating a **skin** condition selected from the group consisting of dry **skin**, photodamaged **skin**, appearance of wrinkles, age spots, aged **skin**, acne sebum control and **skin** lightening, the method comprising applying to the **skin** the composition of claim 1.

L10 ANSWER 3 OF 8 USPATFULL

AB Fatty acid amides in combination with azoles and either **retinol** or **retinyl ester** resulted in a synergistic enhancement in keratinocyte proliferation and synergistic inhibition of keratinocyte differentiation. The effects of the **retinol** or **retinyl esters** in combination with fatty acid amides and azoles were analogous to treatment with **retinoic acid**.

AN 1998:14487 USPATFULL

TI **Skin** care compositions containing fatty acid amides, azoles, and **retinol** or **retinyl ester**

IN Granger, Stewart Paton, Paramus, NJ, United States
Rawlings, Anthony Vincent, Warrington, England
Scott, Ian Richard, Allendale, NJ, United States

PA Elizabeth Arden Co., Division of Conopco, Inc., New York, NY, United States (U.S. corporation)

PI US 5716627 19980210 <--

AI US 1996-638074 19960425 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Venkat, Jyothsan

LREP Mitelman, Rimma

CLMN Number of Claims: 2

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 958

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Skin** care compositions containing fatty acid amides, azoles, and **retinol** or **retinyl ester**

PI US 5716627 19980210 <--

AB Fatty acid amides in combination with azoles and either **retinol** or **retinyl ester** resulted in a synergistic enhancement in keratinocyte proliferation and synergistic inhibition of keratinocyte differentiation. The effects of the **retinol** or **retinyl esters** in combination with fatty acid amides and azoles were analogous to treatment with **retinoic acid**.

SUMM **Retinol** (vitamin A) is an endogenous compound which occurs naturally in the human body and is essential for normal epithelial cell differentiation. Natural and synthetic vitamin A derivatives have been used extensively in the treatment of a variety of **skin**

disorders and have been used as **skin** repair or renewal agents. **Retinoic acid** has been employed to treat a variety **skin** conditions, e.g., acne, wrinkles, psoriasis, age spots and discoloration. See e.g., Vahlquist, A. et al., J. Invest. Dermatol., Vol. 94, Holland D. B. and Cunliffe, W. J. (1990), pp. 496-498; Ellis, C. N. et al., "Pharmacology of **Retinols** in **Skin**", Vasel, Karger, Vol. 3, (1989), pp. 249-252; Lowe, N. J. et al., "Pharmacology of **Retinols** in **Skin**", Vol. 3, (1989), pp. 240-248; PCT Patent Application No. WO 93/19743. **Retinol** and **retinyl esters**, such as retinyl acetate and retinyl palmitate, are easier to formulate/stabilize than **retinoic acid**. Unfortunately, **retinol** and **retinyl esters** are less effective than **retinoic acid** at providing **skin** benefits.

The present invention is based, in part, on the discovery that certain combinations of **retinol** or **retinyl esters** with fatty acid amides and azoles result in a synergistic improvement in keratinocyte proliferation and differentiation. The effects of combination of a fatty acid amide with azole and either **retinol** or a **retinyl ester** were analogous to the effects of **retinoic acid**. This effect was not only greater than the effect of either **retinol/retinyl ester** with a fatty acid amide or of **retinol/retinyl ester** with azole but the three ingredients acted in synergy with each other to promote a **retinoic acid** response. Thus, a mixture of fatty acid amides with **retinol** or **retinyl esters** mimics **retinoic acid** yet is easier to use than **retinoic acid**.

SUMM . . . from about 0.025% to about 35% of a monocarboxylic fatty acid, ester, or amide. The compositions may also include a **retinoid**; Thornfeldt teaches that certain **retinoids**, namely isotretinoin, tretinoin, errerin (all of which are stereoforms of **retinoic acid**) and etretinate (an ester of trimethoxyphenyl **retinoic acid**) have proven efficacy against papulosquamous diseases. PCT Application WO/9325177 (Procter and Gamble) discloses compositions for topical application to **skin** which contain a specific type of acyclic carboxamide coolant and may include **retinoids** such as **retinoic acid** and its derivatives (e.g., cis and trans). PCT application WO/9403156 (Rhone Poulenc) discloses a topical composition containing linoleic acid or a derivative as an active ingredient for treatment and prophylaxis of impure **skin** (e.g., **skin** affected by pimples, pustules, or comedones); the composition may also contain 0.025-0.1 wt. % of tretinoin. European Patent Application No.. . .

SUMM . . . (U.S. Pat. No. 5,216,148) disclose the use of specific complex carboxamides for treating and preventing neoplasms, dermatoses, and aging of **skin**. Van Scott et al. (U.S. Pat. No. 4,380,549) and Yu et al., (U.S. Pat. No. 4,363,815) disclose treatment of acne, dry, flaky, scaly **skin** with a hydroxyacid or the amide thereof. EP 582,458 discloses use of N,N-(1,4C alkyl) lauramide EP 559,304 disclose the use of an amide containing a hydrocarbyl chain of at least 25 carbon atoms as a **skin** smoothening agent. Beauquey et al. (U.S. Pat. No. 5,308,551) disclose a **skin** washing and conditioning composition containing, among other ingredients, a 1-4C alkanolamide of a 8-16C fatty acid. Great Britain Patent Specification. . .

SUMM Compositions containing **retinoids** and azoles nave been described. See for instance Yusuf et al., CA 2,101,101, Cauwenbergh, U.S. Pat. No. 5,476,852 and Keyhani,. . .

SUMM Compositions containing azoles and fatty acid amides are also known. These compositions, however, do not include any **retinoids**. See for instance, WO 95/17175; EP 0 347,199; U.S. Pat. No. 4,867,971; and U.S. Pat. No. 5,348,736.

SUMM The art cited above does not disclose **skin** conditioning compositions based on synergistic combinations of three ingredients: a fatty acid amide, an azole and **retinol** or a **retinyl ester**. None of the art cited above addresses the need for an effective alternative to **retinoic acid**.

SUMM The present invention includes, in part, a **skin** conditioning composition containing:

SUMM (a) from about 0.001% to about 10% of **retinol** or a **retinyl ester**;

SUMM The term "conditioning" as used herein means prevention and treatment of dry **skin**, photodamaged **skin**, appearance of wrinkles, age spots, aged **skin**, increasing stratum corneum flexibility, and generally increasing the quality of **skin**. The composition may be used to improve **skin** desquamation and epidermal differentiation.

SUMM The presence of the fatty acid amide and an azole in the inventive product substantially improves the performance of **retinol** or a **retinyl ester**, i.e., fatty acid amide in combination with azole substantially increases the ability of **retinol** or a **retinyl ester** to affect cellular proliferation and differentiation. The fatty acid amide or an azole has no or little effect on improving **skin** benefit when used alone; a substantial increase in **skin** benefit is only realized when the amide and the azole are combined with **retinol** or a **retinyl ester**. In short, the present invention is based, at least in part, on the discovery of synergistic interaction between **retinol** or a **retinyl ester**, fatty acid amides, and azoles.

SUMM . . . C.sub.8 -C.sub.24 fatty acid, most preferably a mono- or di-alkanolamide of a C.sub.8 -C.sub.24 fatty acid and the azole is **climbazole**.

SUMM . . . present invention, by virtue of including an effective amount of a fatty acid amide and an azole into compositions containing **retinol** or a **retinyl ester**, the performance of the compositions is substantially improved. Alternatively, lower levels of **retinol** or a **retinyl ester** may be included in the composition containing the fatty acid amide and the azole to equal the performance of a. . .

SUMM The inventive compositions contain, as a first essential ingredient, a compound selected from the group consisting of **retinol** or a **retinyl ester**. The term "**retinol**" includes the following isomers of **retinol**: all-trans-**retinol**, 13-cis-**retinol**, 11-cis-**retinol**, 9-cis-**retinol**, 3,4-didehydro-**retinol**. Preferred isomers are all-trans-**retinol**, 13-cis-**retinol**, 3,4-didehydro-**retinol**, 9-cis-**retinol**. Most preferred is all-trans-**retinol**, due to its wide commercial availability.

SUMM **Retinyl ester** is an ester of **retinol**. The term "**retinol**" has been defined above. **Retinyl esters** suitable for use in the present invention are C.sub.1 -C.sub.30 esters of **retinol**, preferably C.sub.2 -C.sub.20 esters, and most preferably C.sub.2, C.sub.3, and C.sub.16 esters

because they are more commonly available. Examples of **retinyl esters** include but are not limited to: retinyl palmitate, retinyl formate, retinyl acetate, retinyl propionate, retinyl butyrate, retinyl valerate, retinyl isovalerate,. . .

SUMM **Retinol** or **retinyl ester** is employed in the inventive composition in an amount of from about 0.001% to about 10%, preferably in an amount. . .

SUMM . . . preferably from 12 to 18 carbon atoms, because longer chain fatty acid amides are more beneficial for conditioning of the **skin**. In the most preferred embodiment of the invention, amides of essential fatty acids are employed because essential fatty acids provide nutrition for the **skin**. Examples of essential fatty acids include but are not limited to linoleic, linolenic, arachidonic, gamma-linolenic, homo-gamma-linolenic, and mixtures thereof. Linoleic. . .

SUMM **Climbazole**, miconazole, bifonazole, econazole, clotrimazole are most preferred. Also suitable for use in the present invention are 1,2,4-triazole, octyl triazole, ketoconazole,. . .

SUMM . . . for the active components in the composition, so as to facilitate their distribution when the composition is applied to the **skin**.

SUMM Optional **Skin** Benefit Materials and Cosmetic Adjuncts

SUMM . . . invention. Various types of active ingredients may be present in cosmetic compositions of the present invention. Actives are defined as **skin** benefit agents other than emollients and other than ingredients that merely improve the physical characteristics of the composition. Although not. . .

SUMM The composition according to the invention is intended primarily as a product for topical application to human **skin**, especially as an agent for conditioning and smoothening the **skin**, and preventing or reducing the appearance of wrinkled or aged **skin**
.

SUMM . . . a small quantity of the composition, for example from 1 to 5 ml, is applied to exposed areas of the **skin**, from a suitable container or applicator and, if necessary, it is then spread over and/or
rubbed into the **skin** using the hand or fingers or a suitable device.

SUMM The topical **skin** treatment composition of the invention can be formulated as a lotion having a viscosity of from 4,000 to 10,000 mPas,.
. .

DETD **Retinoic acid** is more effective than **retinol** at altering keratinocyte differentiation state

DETD A. The effect on incorporation of .sup.3 H-thymidine .mu.g soluble protein 24 hours after the addition of **retinoic acid** or **retinol** at various concentrations was examined. The results that were obtained are summarized in Table 1A.

DETD TABLE 1A

EFFECT OF **RETINOIC ACID** (RA) AND **RETINOL** (ROH) ON KERATINOCYTE THYMIDINE INCORPORATION

mean Thymidine incorp./.mu.g protein .+-. s.d	p value vs	p value vs	p value vs

. . .

DETD All concentrations of **retinoic acid** tested, i.e.,

2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 and 2.5.times.10.sup.-9 M, significantly increased keratinocyte proliferation over both the ethanol control and each of the 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M **retinol** treatments and they did so in a dose dependant manner. This is consistent with **retinoic acid** having a greater stimulatory effect on epithelial proliferation than **retinol**.

DETD B. The effect on Transglutaminase levels after addition of **retinoic acid** and **retinol** was examined. The results that were obtained are summarized in Table 1B.

DETD TABLE 1B

EFFECT OF **RETINOIC ACID** (RA) AND **RETINOL** (ROH) ON KERATINOCYTE TRANSGLUTAMINASE LEVEL

Mean TGase/DNA X 10.sup.-4 .+-. S.D.	p value vs	p value vs	p value vs	p. . .

DETD All concentrations of **retinoic acid** tested, i.e., 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M decreased keratinocyte differentiation over both the ethanol control and each of the **retinol** treatments and did so to a significantly greater extent than each of the corresponding 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M **retinol** treatments. The decrease in transglutaminase level was dose dependent for both **retinoic acid** and **retinol**. This is consistent with **retinoic acid** having a greater inhibitory effect on epithelial differentiation than **retinol**.

DETD LINOLEOYL-DIETHANOLAMIDE (LINOLEOYL-DEA), BIFONAZOLE AND **RETINOL** ACT SYNERGISTICALLY TO ENHANCE KERATINOCYTE PROLIFERATION AND TO INHIBIT DIFFERENTIATION

DETD TABLE 2A

EFFECT OF **RETINOL**, BIFONAZOLE AND LINOLEOYL-MEA ON KERATINOCYTE THYMIDINE INCORPORATION

mean Thymidine incorp..mu.g protein	p value	p value vs. 10.sup.-9	p value vs. 10.sup.-9 . . . .times. 10.sup.-9 M RA	
5569 .+-. 248 (127%)	0.008	0.002	--	* = 0.158 @ = 0.085
2.5 .times. 10.sup.-9 M **Retinal**				
4856 .+-. 217 (111%)	0.105	--	0.038	* = 0.600

@ = 0.403
2.5 .times. 10.sup.-9 M ROH + 10.sup.-8 M. . .
DETD 2.5.times.10.sup.-9 M **retinoic acid** significantly increased keratinocyte thymidine incorporation by 27% over the ethanol control and by 16% over the 2.5.times.10.sup.-9 M **retinol** treatment. Both 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M linoleamide-DEA and 2.5.times.10.sup.-9 M **retinol**+10.sup.-9 M bifonazole had a marginal stimulatory effect on keratinocyte proliferation over **retinol** on its own. However the combination of 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M linoleamide-DEA+10.sup.-9 M bifonazole significantly increased keratinocyte proliferation over both the ethanol and the 2.5.times.10.sup.-8 M **retinol** treatments by 30% and 19% respectively. The combination of 2.5.times.10.sup.-9 M **retinol** +10.sup.-8 M linoleamide-DEA+10.sup.-9 M bifonazole also increased keratinocyte proliferation over the 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M linoleamide-DEA and 2.5.times.10.sup.-9 M **retinol**+10.sup.-9 M bifonazole treatments. Fatty acid amides, bifonazole and **retinol** therefore, act synergistically to increase keratinocyte proliferation to levels which closely resemble the stimulatory effect of **retinoic acid.**

DETD . . . 0.027
-- 0.001
0.001
0.010
(100%)
2.5 .times. 10.sup.8 M RA
0.017 .+-. 0.010 (13%)
0.001
-- 0.001
2.5 .times. 10.sup.8 M **Retinol**
0.111 .+-. 0.023 (84%)
0.066
-- 0.001
0.001
10.sup.8 M LA-MEA + 10.sup.8
0.165 .+-. 0.026 (125%)
0.010
Bifonazole
2.5 .times. 10.sup.8 M. . .
DETD 2.5.times.10.sup.-8 M **retinoic acid** was very effective at repressing keratinocyte TG1 levels i.e. to 13% of contol level. Neither 2.5.times.10.sup.-8 M **retinol** nor 10.sup.-8 M LAMEA+10.sup.-8 M bifonazole had an inhibitory effect on the keratinocyte TG1 level. However 2.5.times.10.sup.-8 M **retinol** +10.sup.-8 M LAMEA+10.sup.-8 M bifonazole repressed keratinocyte TG1 to 42% of control levels. **Retinol,** fatty acid amides and bifonazole therefore act synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid.**

DETD LINOLEOYL-DEA, **CLIMBAZOLE** AND **RETINOL** SYNERGISTICALLY ENHANCED KERATINOCYTE PROLIFERATION AND INHIBITED DIFFERENTIATION

DETD A. The effect of linoleoyl-DEA, **climbazole** and **retinol** on incorporation of .sup.3 H-thymidine was examined. The results that were obtained are summarized in Table 3A.

DETD TABLE 3A

EFFECT OF **RETINOL, CLIMBAZOLE** AND LINOLEOYL-DEA ON

KERATINOCYTE THYMIDINE INCORPORATION

	mean Thymidine incorp/.mu.g protein	p value vs	p value vs	p value vs
				p value. . . .times. 10.sup.7 M RA
	4845 .+-. 95 (130%)	0.001	0.001	--
				* = 0.006
				@ = 0.004
2.5 .times. 10.sup.8 M **Retinol**	3788 .+-. 57 (102%)	0.275	--	0.001
				* = 0.043
				@ = 0.090
2.5 .times. 10.sup.8 M ROH + 10.sup.8 M.			. .	--
				@ = 0.626
2.5 .times. 10.sup.8 M ROH + 10.sup.9 M	4056 .+-. 160 (109%)	0.048	0.090	0.004
				* = 0.626
Climbazole				--
2.5 .times. 10.sup.8 M ROH + 10.sup.8 M LADEA	4781 .+-. 196 (129%)	0.002	0.002	0.697
				* = 0.023
+ 10.sup.9 M **Climbazole**				@ = 0.015

---

n = 3
* = p value vs 2.5 .times. 10.sup.8 M ROH + 10.sup.8 M LADEA
@ = p value vs 2.5 .times. 10.sup.8 M ROH + 10.sup.9 M **Climbazole**

DETD 2.5.times.10.sup.-7 M **retinoic acid** significantly increased keratinocyte thymidine incorporation by 30% over the ethanol control and by 28% over the 2.5.times.10.sup.-8 M **retinol** treatment. Both 2.5.times.10.sup.-8 M **retinol**+10.sup.-8 M linoleamide-DEA and 2.5.times.10.sup.-8 M **retinol**+10.sup.-9 M **climbazole** had a significant stimulatory effect on keratinocyte proliferation over the control and **retinol** on its own. However the combination of 2.5.times.10.sup.-8 M **retinol**+10.sup.-8 M linoleamide-DEA+10.sup.-9 M **climbazole** significantly increased keratinocyte proliferation over both the ethanol and the 2.5.times.10.sup.-8 M **retinol** treatments by 29% and 27% respectively. Most significantly the combination of 2.5.times.10.sup.-8 M **retinol**+10.sup.-8 M linoleamide-DEA+10.sup.-9 M **climbazole** also significantly increased keratinocyte proliferation over both the 2.5.times.10.sup.-8 M **retinol** +10.sup.-8 M linoleamide-DEA and 2.5.times.10.sup.-8 M **retinol** +10.sup.-9 M **climbazole** treatments by 17% and 20% respectively. **Retinol**, linoleamide-DEA and **climbazole** therefore, act synergistically to increase keratinocyte proliferation to levels which closely resemble the stimulatory effect of **retinoic**

acid.

DETD TABLE 3B

EFFECT OF **RETINOL, CLIMBAZOLE** AND LINOLEOYL-DEA ON KERATINOCYTETGASE LEVELS

mean TGase/DNA .times. 10.sup.4	p value vs.	p value vs.	p value vs.	p value (% .+-. s.d (29%)
2.5 .times. 10.sup.9 M RA	0.027	0.000	0.000	0.000
0.84 .+-. 0.59 (55%)	0.553	0.000	0.000	0.000
2.5 .times. 10.sup.9 M **Retinol**				
1.96 .+-. 0.33 (129%)	0.000	--	0.000	0.000
2.5 .times. 10.sup.9 M ROH + 10.sup.8 M LA-DEA				
1.59 .+-. 0.28 (105%)	0.000	0.000	--	0.360
2.5 .times. 10.sup.9 M ROH + 10.sup.8 M **Climbazole**				
1.66 .+-. 0.42 (109%)	0.000	0.000	0.360	--
2.5 .times. 10.sup.9 M ROH + 10.sup.8 LA-DEA + 10.sup.8 M **Climbazole**				
1.27 .+-. 0.51 (83%)	0.000	0.000	0.000	0.000
2.5 .times. 10.sup.9 M ROH +10.sup.8 M LA-DEA + 10.sup.7 M **Climbazole**				
1.10 = 0.40 (72%)	0.009	0.000	0.000	0.000

n = 6

DETD 2.5.times.10.sup.-7 M **retinoic acid** was very effective at repressing keratinocyte TG1 levels (to 29%) of contol level whereas the more dilute 2.5.times.10.sup.-9 M **retinoic acid** was not as effective but still inhibited TG1 levels by 55%. 2.5.times.10.sup.-9 M **retinol**, 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M LADEA and 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M **climbazole** had no inhibitory effect on the keratinocyte TG1 level. However 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M LADEA+10.sup.-8 M **climbazole** significantly repressed keratinocyte TG1 to 83% of control levels. This inhibition was significantly greater than the control, ROH alone, ROH+LADEA and ROH+**climbazole** indicating that the three ingredients, i.e., ROH, LADEA and **climbazole** act synergistically to inhibit keratinocyte TG1 levels. This effect was even greater when the **climbazole** concentration was increased by 10.times., i.e., 2.5.times.10.sup.-9 M+10.sup.-8 M LADEA+10.sup.-7 M **climbazole**, which resulted in this combination inhibiting TG1 levels to 72% of control. **Retinol**, fatty acid amides and **climbazole** therefore act synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid.**

DETD CLOTRIMAZOLE, LINOLEAMIDE-MEA AND **RETINOL** SYNERGISTICALLY ENHANCED KERATINOCYTE PROLIFERATION

DETD TABLE 4

EFFECT OF **RETINOL**, LINOLEAMIDE-MEA AND CLOTRIMAZOLE ON KERATINOCYTE THYMIDINE INCORPORATION

Treatment. . . .times. 10.sup.9 M	mean Thymidine incorp/.mu.g protein	p value vs	p value vs	p value vs
RA	1.28 .+-. 0.09 (128%)	0.001	0.002	--
2.5 .times. 10.sup.9 M **Retinol**	1.13 .+-. 0.09 (113%)	0.041	--	0.002
2.5 .times. 10.sup.9 M ROH + 10.sup.8 M				

* = 0.001
@ = 0.041

* = 0.176
@ = 0.853

. . .

DETD 2.5.times.10.sup.-9 M **retinoic acid** significantly increased keratinocyte thymidine incorporation by 28% over the ethanol control and by 15% over the 2.5.times.10.sup.-9 M **retinol** treatment. Both 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M linoleamide-MEA and 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M clotrimazole had a stimulatory effect on keratinocyte proliferation over the control but this effect was no greater than **retinol** on its own. However the combination of 2.5.times.10.sup.-9 M **retinol** +10.sup.-8 M linoleamide-MEA+10.sup.-8 M clotrimazole significantly increased keratinocyte proliferation over both the ethanol control and the 2.5.times.10.sup.-8 M **retinol** treatment by 29% and 16% respectively. Most unexpectedly the combination of 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M linoleamide-MEA+10.sup.-8 M clotrimazole also significantly increased keratinocyte proliferation over both the 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M linoleamide-MEA and 2.5.times.10.sup.-9 M **retinol**+10.sup.-8 M clotrimazole treatments by 21% and 17% respectively. **Retinol**, linoleamide-MEA and clotrimazole therefore, act synergistically to increase keratinocyte proliferation to levels which closely resemble the stimulatory effect of **retinoic acid**.

DETD Examples 1-4 demonstrate that **retinoic acid**, in a dose dependant manner, increased thymidine incorporation and decreased transglutaminase I levels in **skin** keratinocytes. In other words **retinoic acid** increased keratinocyte proliferation and decreased keratinocyte differentiation. In Examples 1-4, **retinoic acid** was used as positive control and reference compound against which the other compounds under analysis were compared. **Retinol** was significantly less effective than **retinoic acid** at inhibiting keratinocyte differentiation and completely ineffective at increasing keratinocyte proliferation.

DETD The unexpected results of Examples 1-4, however, were that the effect of

retinol on cultured keratinocytes can be enhanced to levels approaching those of **retinoic acid** by combining **retinol** or **retinyl ester** with a fatty acid amide and an azole, although an azole and a fatty acid amide each exerts little or. . . benefit on its own. The results documented above demonstrate that fatty acid amides in combination with azoles act synergistically with **retinol** or **retinyl ester**, both to increase keratinocyte proliferation and to decrease keratinocyte differentiation, mimicking the effect of **retinoic acid**.

DETD The unexpected result of this study was that the effect of **retinol** on cultured keratinocytes can be enhanced to levels approaching those of **retinoic acid** by combining **retinol** with a fatty acid amide and an azole. This effect was not only greater than the effect of either **retinol**+fatty acid amide or of **retinol**+azole but the three ingredients acted in synergy with each other to promote a **retinoic acid** type response.

DETD The results documented above demonstrate that fatty acid amides and azoles act synergistically with **retinol** both to increase keratinocyte proliferation and decrease keratinocyte differentiation, mimicking the effect of **retinoic acid**.

DETD

	% w/w
Retinol	0.5
Miconazole	1
Linoleoyl-diethanolamide	5
Fully hydrogenated coconut oil	3.9
Brij 92*	5
Bentone 38	0.5
MgSO.sub.4 7H.sub.2 O	0.3
Butylated hydroxy toluene	0.01
Perfume	qs
Water	to 100

. . .

DETD

	% w/w
Retinol	0.15
Clotrimazole	2
Cocoyl diethanolamide	1
Mineral oil	4
Brij 56*	4
Alfol 16RD*	4
Triethanolamine	0.75
Butane-1,3-diol	3
Xanthan gum	0.3
Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

. . .

DETD

% w/w

Retinol	0.15
Palmitoyl-monoethanolamide	0.1
Climbazole	2
Ethanol	40
Antioxidant	0.1
Perfume	qs
Water	to 100

DETD

% w/w

Retinol	0.01
Linoleoyl monoethanolamide	0.1
Climbazole	0.1
Silicone oil 200 cts	7.5
Glycerylmonostearate	3
Cetosteryl alcohol	1.6
Polyoxyethylene-(20)-cetyl alcohol	1.4
Xanthan gum	0.5
Parsol 1789	1.5
Octyl methoxycinnate (PARSOL MCX)	7
Perfume	qs
Color	qs
Water. . .	

DETD This example illustrates a non-aqueous **skin** care composition incorporating the inventive combination.

DETD

% w/w

Retinol palmitate	0.15
Linoleoyl diethanolamide	1
Miconazole	0.1
Silicone gum SE-30.sup.1	10
Silicone fluid 345.sup.2	20
Siiicone fluid 344.sup.3	55.79
Squalene	10
Linoleic acid	0.01
Cholesterol	0.03
2-hydroxy-n-octanoic acid	0.7
Vitamin. . .	

CLM What is claimed is:

1. A **skin** conditioning composition comprising (a) from about 0.001% to about 10% of a compound selected from the group consisting of **retinol**; (b) from about 0.0001% to about 50% of an azole selected from the group consisting of **climbazole**, miconazole, bifonazole, clotrimazole, econazole; (c) from about 0.0001% to about 50% of a fatty acid amide selected from the group. . .

2. A method of treating a **skin** condition selected from the group consisting of dry **skin**, photodamaged **skin**,

appearance of wrinkles, age spots and aged **skin**, the method comprising applying to the **skin** the composition of claim 1.

IT 68-26-8, Retinol 68-26-8D, Retinol, esters 79-81-2, Retinyl palmitate
127-47-9, Retinyl acetate 302-79-4, Retinoic acid. 631-89-0, Retinyl linoleate 7069-42-3, Retinyl propionate 22916-47-8, Miconazole 23593-75-1, Clotrimazole 27220-47-9, Econazole **38083-17-9**, Climbazole 56863-02-6 60628-96-8, Bifonazole 68171-52-8
(skin care compns. contg. retinol or retinyl ester)

L10 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS

AB Fatty acid amides in combination with azoles and either **retinol** or **retinyl ester** resulted in a synergistic enhancement in keratinocyte proliferation and synergistic inhibition of keratinocyte differentiation. The effects of the **retinol** or **retinyl esters** in combination with fatty acid amides and azoles were analogous to treatment with **retinoic acid**. A combination of 2.5x10-9 **retinol**, 10-8 linoleoyl diethanolamide, and 10-9 M bifonazole had similar activity on the proliferation of cultured keratinocytes. A lotion contained retinyl palmitate 0.15, linoleoyl monoethanolamide 0.1, **climbazole** 1, ethanol 40, butylated hydroxy toluene 0.1, perfume q.s., and water q.s. 100%.

AN 1997:720065 CAPLUS

DN 127:362474

TI **Skin** care compositions containing **retinol** or **retinyl ester**

IN Granger, Stewart Paton; Rawlings, Anthony Vincent; Scott, Ian Richard

PA Unilever Plc, UK; Unilever N.V.

SO Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 803248	A2	19971029	EP 1997-302459	19970410 <--
	EP 803248	A3	19971217		
	EP 803248	B1	20020828		
	R: CH, DE, ES, FR, GB, IT, LI, NL, SE				
	US 5716627	A	19980210	US 1996-638074	19960425 <--
	AU 9719018	A1	19971030	AU 1997-19018	19970409 <--
	AU 709425	B2	19990826		
	CA 2202338	AA	19971025	CA 1997-2202338	19970410 <--
	JP 10036248	A2	19980210	JP 1997-107595	19970424 <--
	CN 1169854	A	19980114	CN 1997-112973	19970425 <--
	BR 9701946	A	19980915	BR 1997-1946	19970425 <--
PRAI	US 1996-638074	A	19960425		

OS MARPAT 127:362474

TI **Skin** care compositions containing **retinol** or **retinyl ester**

PI EP 803248 A2 **19971029**

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 803248	A2	19971029	EP 1997-302459	19970410 <--
	EP 803248	A3	19971217		
	EP 803248	B1	20020828		
	R: CH, DE, ES, FR, GB, IT, LI, NL, SE				
	US 5716627	A	19980210	US 1996-638074	19960425 <--
	AU 9719018	A1	19971030	AU 1997-19018	19970409 <--
	AU 709425	B2	19990826		

CA 2202338	AA	19971025	CA 1997-2202338	19970410	<--
JP 10036248	A2	19980210	JP 1997-107595	19970424	<--
CN 1169854	A	19980114	CN 1997-112973	19970425	<--
BR 9701946	A	19980915	BR 1997-1946	19970425	<--

AB Fatty acid amides in combination with azoles and either **retinol** or **retinyl ester** resulted in a synergistic enhancement in keratinocyte proliferation and synergistic inhibition of keratinocyte differentiation. The effects of the **retinol** or **retinyl esters** in combination with fatty acid amides and azoles were analogous to treatment with **retinoic acid**. A combination of 2.5x10-9 **retinol**, 10-8 linoleoyl diethanolamide, and 10-9 M bifonazole had similar activity on the proliferation of cultured keratinocytes. A lotion contained retinyl palmitate 0.15, linoleoyl monoethanolamide 0.1, **climbazole** 1, ethanol 40, butylated hydroxy toluene 0.1, perfume q.s., and water q.s. 100%.

ST **skin** cosmetic **retinol** ester keratinocyte proliferation; lotion retinyl palmitate linoleoyl monoethanolamide **climbazole**

IT Amides, biological studies
Amides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(N-(hydroxyalkyl); **skin** care compns. contg. **retinol** or **retinyl ester**)

IT Cosmetics
(creams; **skin** care compns. contg. **retinol** or **retinyl ester**)

IT Amides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(fatty; **skin** care compns. contg. **retinol** or **retinyl ester**)

IT **Skin**
(keratinocyte, proliferation of; **skin** care compns. contg. **retinol** or **retinyl ester**)

IT Cell proliferation
(keratinocyte; **skin** care compns. contg. **retinol** or **retinyl ester**)

IT Cosmetics
(lotions; **skin** care compns. contg. **retinol** or **retinyl ester**)

IT Heterocyclic compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(nitrogen, five-membered; **skin** care compns. contg. **retinol** or **retinyl ester**)

IT Sunscreens
(**skin** care compns. contg. **retinol** or **retinyl ester**)

IT 68-26-8, **Retinol** 68-26-8D, **Retinol**, esters
79-81-2, Retinyl palmitate 127-47-9, Retinyl acetate 302-79-4,

Retinoic acid. 631-89-0, Retinyl linoleate
7069-42-3, Retinyl propionate 22916-47-8, Miconazole 23593-75-1,
Clotrimazole 27220-47-9, Econazole **38083-17-9**,
Climbazole 56863-02-6 60628-96-8, Bifonazole 68171-52-8
RL: BAC (Biological activity or effector, except adverse); BSU
(Biological
study, unclassified); BUU (Biological use, unclassified); BIOL
(Biological
study); USES (Uses)
(**skin** care compns. contg. **retinol** or
retinyl ester)

L10 ANSWER 5 OF 8 USPATFULL
AB Melinamide in combination with either **retinol** or **retinyl ester** resulted in a synergistic enhancement in keratinocyte proliferation. The effects of the **retinol** or **retinyl esters** in combination with fatty acid amides were analogous to treatment with **retinoic acid**.
AN 97:112169 USPATFULL
TI **Skin** care compositions containing melinamide and a **retinoid**
IN Granger, Stewart Paton, Paramus, NJ, United States
Rawlings, Anthony Vincent, Warrington, NJ, United States
Scott, Ian Richard, Allendale, NJ, United States
PA Elizabeth Arden Co., Division of Conopco, Inc., New York, NY, United States (U.S. corporation)
PI US 5693330 19971202 <--
AI US 1996-636811 19960425 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Venkat, Jyothsan
LREP Mitelman, Rimma
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 571
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI **Skin** care compositions containing melinamide and a **retinoid**
PI US 5693330 19971202 <--
AB Melinamide in combination with either **retinol** or **retinyl ester** resulted in a synergistic enhancement in keratinocyte proliferation. The effects of the **retinol** or **retinyl esters** in combination with fatty acid amides were analogous to treatment with **retinoic acid**.
SUMM The invention relates to **skin** care compositions containing melinamide and a **retinoid**, preferably **retinol** or **retinyl ester**.
SUMM **Retinol** (vitamin A) is an endogenous compound which occurs naturally in the human body and is essential for normal epithelial cell differentiation. Natural and synthetic vitamin A derivatives have been used extensively in the treatment of a variety of **skin** disorders and have been used as **skin** repair or renewal agents. **Retinoic acid** has been employed to treat a variety of **skin** conditions, e.g., acne, wrinkles, psoriasis, age spots and discoloration. See e.g., Vahlquist, A. et al., J. Invest. Dermatol., Vol. 94, Holland D. B. and Cunliffe, W. J. (1990), pp. 496-498; Ellis, C. N. et al., "Pharmacology of **Retinols** in **Skin**", Vasel, Karger, Vol. 3, (1989), pp. 249-252; Lowe, N. J. et al., "Pharmacology of **Retinols** in **Skin**", Vol. 3, (1989),

pp. 240-248; PCT Patent Application No. WO 93/19743. **Retinol** and **retinyl esters**, such as retinyl acetate and retinyl palmitate, are easier to formulate/stabilize than **retinoic acid**. Unfortunately, **retinol** and **retinyl esters** are less effective than **retinoic acid** at providing **skin** benefits. The present invention is based, in part, on the discovery that a combination of **retinol** or **retinyl esters** with melinamide results in a synergistic improvement in keratinocyte proliferation. The effects of melinamide combined with **retinol** or a **retinyl ester** were analogous to the effects of **retinoic acid**. Thus, a mixture of melinamide with **retinol** or **retinyl esters** mimics **retinoic acid** yet is easier to use than **retinoic acid**.

SUMM . . . from about 0.025% to about 35% of a monocarboxylic fatty acid, ester, or amide. The compositions may also include a **retinoid**; Thornfeldt teaches that certain **retinoids**, namely isotretinoin, tretinoin, etretin (all of which are stereoforms of **retinoic acid**) and etretinate (an ester of trimethoxyphenyl **retinoic acid**) have proven efficacy against papulosquamous diseases. PCT Application WO/9325177 (Procter and Gamble) discloses compositions for topical application to **skin** which contain a specific type of acyclic carboxamide coolant and may include **retinoids** such as **retinoic acid** and its derivatives (e.g., cis and trans). PCT application WO/9403156 (Rhone Poulenc) discloses a topical composition containing linoleic acid or a derivative as an active ingredient for treatment and prophylaxis of impure **skin** (e.g., **skin** affected by pimples, pustules, or comedones); the composition may also contain 0.025-0.1 wt. % of tretinoin. European Patent Application No.. . .

SUMM . . . (U.S. Pat. No. 5,216,148) disclose the use of specific complex carboxamides for treating and preventing neoplasms, dermatoses, and aging of **skin**. Van Scoff et al. (U.S. Pat. No. 4,380,549) and Yu et al., (U.S. Pat. No. 4,363,815) disclose treatment of acne, dry, flaky, scaly **skin** with a hydroxyacid or the amide thereof. EP 0 582 458 discloses use of N,N-(1,4 C alkyl) lauramide. EP 0. . . 559 304 disclose the use of an amide containing a hydrocarbyl chain of at least 25 carbon atoms as a **skin** smoothening agent. Beauquey et al. (U.S. Pat. No. 5,308,551) disclose a **skin** washing and conditioning composition containing, among other ingredients, a 1-4 C alkanolamide of a 8-16 C fatty acid. Great Britain. . .

SUMM The art cited above does not disclose **skin** conditioning compositions based on synergistic combinations of melinamide with **retinol** or a **retinyl ester**. None of the art cited above addresses the need for an effective alternative to **retinoic acid**.

SUMM Accordingly, it is an object of the present invention to provide a **skin** conditioning composition containing a combination of **retinol** or a **retinyl ester** with melinamide.

SUMM It is another object of the invention to provide a method of conditioning **skin** with a composition containing as an active system a mixture of melinamide with **retinol** or a **retinyl ester**.

SUMM It is yet another object of the invention to provide a substitute for **retinoic acid** in cosmetic compositions.

SUMM The above objects are attained by the present invention which includes, in part, a **skin** conditioning composition containing:

SUMM (a) from about 0.001% to about 10% of a **retinoid** selected from the group consisting of **retinol**, a **retinyl ester**, and **retinoic acid**;

SUMM The term "conditioning" as used herein means prevention and treatment of dry **skin**, photodamaged **skin**, appearance of wrinkles, age spots, aged **skin**, acne, **skin** lightening psoriasis, atopic dermatosis, increasing stratum corneum flexibility, and generally increasing the quality of **skin**. The composition may be used to improve **skin** desquamation and cellular proliferation.

SUMM The presence of melinamide in the inventive product substantially improves the performance of **retinol** or a **retinyl ester**, i.e., melinamide substantially increases the ability of **retinol** or a **retinyl ester** to affect cellular proliferation. Melinamide has no or little effect on improving **skin** benefit when used alone; a substantial increase in **skin** benefit is only realized when melinamide is combined with **retinol** or a **retinyl ester**. In short, the present invention is based, at least in part, on the discovery of synergistic interaction between **retinol** or a **retinyl ester** and melinamide.

SUMM In a preferred embodiment of the invention, a **retinoid** is selected from the group consisting of **retinol** or a **retinyl ester**. According to the present invention, by virtue of including an effective amount of melinamide into compositions containing **retinol** or a **retinyl ester**, the performance of the compositions is substantially improved. Alternatively, lower levels of **retinol** or a **retinyl ester** may be included in the composition containing melinamide to equal the performance of a similar formulation without the amide.

SUMM The inventive compositions contain, as a first essential ingredient, a compound selected from the group consisting of **retinol**, a **retinyl ester**, or **retinoic acid**.

SUMM The term **"retinol"** includes the following isomers of **retinol**: all-trans-**retinol**, 13-cis-**retinol**, 11-cis-**retinol**, 9-cis-**retinol**, 3,4-didehydro-**retinol**. Preferred isomers are all-trans-**retinol**, 13-cis-**retinol**, 3,4-didehydro-**retinol**, 9-cis-**retinol**. Most preferred is all-trans-**retinol**, due to its wide commercial availability.

SUMM **Retinyl ester** is an ester of **retinol**. The term **"retinol"** has been defined above. **Retinyl esters** suitable for use in the present invention are C.sub.1 -C.sub.30 esters of **retinol**, preferably C.sub.2 -C.sub.20 esters, and most preferably C.sub.2, C.sub.3, and C.sub.16 esters because they are more commonly available. Examples of **retinyl esters** include but are not limited to: retinyl palmirate, retinyl formate, retinyl acetate, retinyl propionate, retinyl butyrate, retinyl valerate, retinyl isovalerate,. . .

SUMM The term **"retinoic acid"** includes the following isomers of **retinoic acid**, all-trans-**retinoic acid**, 9-cis-**retinoic acid**, 13-cis-**retinoic acid**, all-trans-3,4-didehydro-**retinoic acid**, 13-cis-3,4-didehydroretinoic acid, 9-cis-3,4-didehydroretinoic acid, 9,13-di-cis-3,4-didehydroretinoic acid, 5,6-epoxyretinoic acid, 5,8-epoxyretinoic acid, 4-oxoretinoic acid, 4-oxo-13-cis-**retinoic acid**.

SUMM The **retinoid** is employed in the inventive composition in an amount of from about 0.001% to about 10%, preferably in an amount. . .

SUMM Optional **Skin** Benefit Materials and Cosmetic Adjuncts

SUMM . . . invention. Various types of active ingredients may be present in cosmetic compositions of the present invention. Actives are defined as **skin** or hair benefit agents other than emollients and other than ingredients that merely improve the physical characteristics of the composition.. . .

SUMM Yet another preferred optional ingredient is selected from azoles, e.g., **climbazole**, bifonazole, clotrimazole, ketoconazole, miconazole, econazole, itraconazole, fiuconazole, terconazole, butoconazole, sulconazole, lionazole and mixtures thereof.

SUMM The composition according to the invention is intended primarily as a product for topical application to human **skin**, especially as an agent for conditioning and smoothening the **skin**, and preventing or reducing the appearance of wrinkled or aged **skin** .

SUMM . . . a small quantity of the composition, for example from 1 to 5 ml, is applied to exposed areas of the **skin**, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the **skin** using the hand or fingers or a suitable device.

SUMM The topical **skin** treatment composition of the invention can be formulated as a lotion having a viscosity of from 4,000 to 10,000 mPas,. . .

DETD **Retinoic Acid** is More Effective Than **Retinol** at Increasing Keratinocyte Proliferation

DETD A. The effect on incorporation of .sup.3 H-thymidine .mu.g soluble protein 24 hours after the addition of **retinoic acid** or **retinol** at various concentrations was examined. The results that were obtained are summarized in Table 1.

DETD TABLE 1

Effect of **Retinoic Acid** (RA) and **Retinol** (ROH) on Keratinocyte Thymidine Incorporation

mean Thymidine incorp./.mu.g protein .+-. s.d | p value vs | p value vs | p value vs

. . .

DETD All concentrations of **retinoic acid** tested, i.e., 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 and 2.5.times.10.sup.-9 M, significantly increased keratinocyte proliferation over both the ethanol control and each of the 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M **retinol** treatments and they did so in a dose dependant manner. This is consistent with **retinoic acid** having a greater stimulatory effect on epithelial proliferation than **retinol**.

DETD Melinamide and **Retinol** Act Synergistically to Enhance Keratinocyte Proliferation

DETD TABLE 2

Effect of **Retinol** and Melinamide on
Keratinocyte Thymidine Incorporation

	p value vs	p value vs	p value vs	p. . . 10.sup.-8 M
mean Thymidine incorp/.mu.g protein .+-.				
6711 .+-. 402 (130%)	0.004	0.025	--	--
RA 2.5 .times. 10.sup.-8 M 3956 .+-. 1303 (76%)	0.185	--	0.025	--
Retinol 10.sup.-7 M 4695 .+-. 324 (91%)	0.115	--	--	--
Melinamide 2.5 .times. 10.sup.-8 M 5776 .+-. 265 (112%)	0.040	0.077	0.028	0.011

ROH. . .

DETD 2.5.times.10.sup.-8 M **retinoic acid** significantly increased keratinocyte thymidine incorporation by 30% over both the ethanol control and the 2.5.times.10.sup.-8 M **retinol** treatment. 10.sup.-7 M melinamide had no effect on keratinocyte proliferation on its own. However, the combination of 2.5.times.10.sup.-8 M **retinol**+10.sup.-7 M melinamide significantly increased keratinocyte proliferation over both the ethanol and the 2.5.times.10.sup.-8 M **retinol** treatments by 12% and 36% respectively. Melinamide and **retinol** therefore, act synergistically to increase keratinocyte proliferation mimicking the stimulatory effect of **retinoic acid**.

DETD The effect of melinamide and the **retinyl ester** (retinyl palmitate) on incorporation of .sup.3 H-thymidine was examined.

The results that were obtained are summarized in Table 3.

DETD TABLE 3

Effect of **Retinol** and Melinamide on
Keratinocyte Thymidine Incorporation

	p value vs	p value vs.	p value	p value
mean Thymidine incorp/.mu.g protein .+-.				

DETD 2.5.times.10.sup.-7 M **retinoic acid** significantly increased keratinocyte thymidine incorporation over both the ethanol

control and the 2.5.times.10.sup.-7 M retinyl palmitate treatment by 38%. 10.sup.-7. . . keratinocyte proliferation over both the ethanol (by 16%) and the 2.5.times.10.sup.-7 M retinyl palmitate control treatments (by 12%). Melinamide and **retinol** therefore, act synergistically to increase keratinocyte proliferation mimicking the stimulator/effect of **retinoic acid.**

DETD Examples 1-3 demonstrate that **retinoic acid,** in a dose dependent manner, increased thymidine incorporation in **skin** keratinocytes. In other words **retinoic acid** increased keratinocyte proliferation. In Examples 1-3, **retinoic acid** was used as positive control and reference compound against which the other compounds under analysis were compared. **Retinol** was completely ineffective at increasing keratinocyte proliferation.

DETD The unexpected results of Examples 1-3, however, were that the effect of **retinol** on cultured keratinocytes can be enhanced to levels approaching those of **retinoic acid** by combining **retinol** or **retinyl ester** with melinamide--a compound which exerts little or no benefit on its own. The results documented above demonstrate that melinamide acts synergistically with **retinol** or **retinyl ester,** to increase keratinocyte proliferation, mimicking the effect of **retinoic acid.**

DETD

	% w/w
Retinol	0.5
Fully hydrogenated coconut oil	3.9
Melinamide	5
Brij 92*	5
Bentone 38	0.5
MgSO.sub.4 7H.sub.2 O	0.3
Butylated hydroxy toluene	0.01
Perfume	qs
Water	to 100

*Brij. . .

DETD

	% w/w
Retinoic acid	0.15
Mineral oil	4
Melinamide	1
Brij 56*	4
Alfol 16RD*	4
Triethanolamine	0.75
Butane-1,3-diol	3
Xanthan gum	0.3
Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

*Brij 56. . .

DETD

% w/w

Retinol 0.15
Melinamide
0.1
Ethanol 40
Antioxidant
0.1
Perfume qs
Water to 100

DETD

	% w/w
Retinol	0.01
Melinamide	0.1
Silicone oil 200 cts	7.5
Glycerylmonostearate	3
Cetosteryl alcohol	1.6
Polyoxyethylene-(20)-cetyl alcohol	1.4
Xanthan gum	0.5
Parsol 1789	1.5
Octyl methoxycinnate (PARSOL MCX)	7
Perfume	qs

Color. . .

DETD This example illustrates a non-aqueous **skin** care composition incorporating the inventive combination.

DETD

	% w/w
Retinoic acid	0.15
Melinamide	1
Silicone gum SE-30.sup.1	10
Silicone fluid 345.sup.2	20
Silicone fluid 344.sup.3	55.79
Squalene	10
Linoleic acid	0.01
Cholesterol	0.03
2-hydroxy-n-octanoic acid	0.7
Vitamin E linoleate	0.5

Herbal. . .

CLM What is claimed is:

1. A **skin** conditioning composition comprising (a) from about 0.001% to about 10% of a compound selected from the group consisting of **retinoic acid, retinol** and a **retinyl ester;** (b) from about 0.0001% to about 50% of melinamide; and (c) a cosmetically acceptable vehicle.

3. The composition of claim 1 wherein ingredient (a) is **retinol** .

4. The composition of claim 1 wherein ingredient (a) is a **retinyl ester.**

5. A method of treating a **skin** condition selected from the group consisting of dry **skin,** photodamaged **skin,**

wrinkles, age spots, aged **skin**, acne, **skin** lightening, psoriasis and atopic dermatosis, the method comprising applying to the **skin** the composition of claim 1.

L10 ANSWER 6 OF 8 USPATFULL

AB Quercetin and/or naringenin in combination with either **retinol** or **retinyl ester** resulted in a synergistic inhibition of keratinocyte differentiation. The effects of the **retinol** or **retinyl esters** in combination with naringenin and/or quercetin were analogous to treatment with **retinoic acid**.

AN 97:80920 USPATFULL

TI **Skin** care compositions containing naringenin and/or quercetin and a **retinoid**

IN Burger, Allan Robert, Passaic, NJ, United States
Granger, Stewart Paton, Paramus, NJ, United States
Scott, Ian Richard, Allendale, NJ, United States

PA Chesebrough-Pond's USA Co., Division of Conopco, Inc., Greenwich, CT, United States (U.S. corporation)

PI US 5665367 19970909 <--

AI US 1996-722540 19960927 (8)

DT Utility

FS Granted

EXNAM Primary Examiner: Page, Thurman M.; Assistant Examiner: Faulkner, D.

LREP Mitelman, Rimma

CLMN Number of Claims: 6

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 703

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI **Skin** care compositions containing naringenin and/or quercetin and a **retinoid**

PI US 5665367 19970909 <--

AB Quercetin and/or naringenin in combination with either **retinol** or **retinyl ester** resulted in a synergistic inhibition of keratinocyte differentiation. The effects of the **retinol** or **retinyl esters** in combination with naringenin and/or quercetin were analogous to treatment with **retinoic acid**.

SUMM The invention relates to **skin** care compositions containing specific flavonoids and a **retinoid**, preferably **retinol** or **retinyl ester**.

SUMM **Retinol** (vitamin A) is an endogenous compound which occurs naturally in the human body and is essential for normal epithelial cell differentiation. Natural and synthetic vitamin A derivatives have been used extensively in the treatment of a variety of **skin** disorders and have been used as **skin** repair or renewal agents. **Retinoic acid** has been employed to treat a variety of **skin** conditions, e.g., acne, wrinkles, psoriasis, age spots and discoloration. See e.g., Vahlquist, A. et al., J. Invest. Dermatol., Vol. 94, Holland D. B. and Cunliffe, W. J. (1990), pp. 496-498; Ellis, C. N. et al., "Pharmacology of **Retinols** in **Skin**", Vasel, Karger, Vol. 3, (1989), pp. 249-252; Lowe, N. J. et al., "Pharmacology of **Retinols** in **Skin**", Vol. 3, (1989), pp. 240-248; PCT Patent Application No. WO 93/19743. It is believed that the use of **retinol** or esters of **retinol** would be preferred over **retinoic acid**. **Retinol** is an endogenous compound which occurs naturally in the human body and is

essential for normal epithelial cell differentiation. **Retinol** is also considered much safer than **retinoic acid**. Esters of **retinol** hydrolyze in-vivo to produce **retinol** . **retinol** and **retinyl esters** are considered ,safer than **retinoic acid**. Unfortunately, **retinol** and **retinyl esters** are less effective than **retinoic acid** at providing **skin** benefits.

SUMM The present invention is based, in part, on the discovery that a combination of **retinol** or **retinyl esters** with specific flavonoids results in a synergistic inhibition in keratinocyte differentiation. The effects of the flavonoids (specifically, naringenin and quercetin) combined with **retinol** or a **retinyl ester** were analogous to the effects of **retinoic acid**. Thus, a mixture of the specific flavonoids with **retinol** or **retinyl esters** mimics **retinoic acid** yet is easier and safer to use than **retinoic acid**.

SUMM . . . lauroyl methionate and flavonoids (including naringenin and quercetin) to inhibit free radical formation. Compositions may also include .beta.-carotene (precursor of **retinol**). FR 2 687 572A discloses certain flavonoids (including naringenin) for protection of **skin** from singlet oxygen. .beta.-carotene or derivatives thereof may also be included. Meadowsweet extract containing flavonoids as radical scavengers is disclosed. . . treatment of acne with naringin and naringenin. These documents do not appear to disclose naringenin or quercetin in combination with **retinol** or **retinyl esters**, or the ability of such combinations to mimic the effect of **retinoic acid**.

SUMM The art cited above does not disclose **skin** conditioning compositions based on synergistic combinations of naringenin or quercetin with **retinol** or a **retinyl ester**. None of the art cited above addresses the need for an effective alternative to **retinoic acid**.

SUMM The above objects are attained by the present invention which includes, in part, a **skin** conditioning composition containing:

SUMM (a) from about 0.001% to about 10% of a **retinoid** selected from the group consisting of **retinol**, a **retinyl ester**, and mixtures thereof;

SUMM The term "conditioning" as used herein means prevention and treatment of dry **skin**, photodamaged **skin**, appearance of wrinkles, age spots, aged **skin**, acne, **skin** lightening, psoriasis, atopic dermatosis, increasing stratum corneum flexibility, controlling sebum excretion and generally increasing the quality of **skin**. The composition may be used to improve **skin** desquamation and cellular proliferation.

SUMM The presence of the flavonoid in the inventive product substantially improves the performance of **retinol** or a **retinyl ester**, i.e., the flavonoid substantially increases the ability of **retinol** or a **retinyl ester** to affect cellular proliferation. The flavonoid has no or little effect on improving **skin** benefit when used alone; a substantial increase in **skin** benefit is only realized when the flavonoid is combined with **retinol** or a **retinyl ester**. In short, the present invention is based, at least in part, on the discovery of synergistic interaction between **retinol** or a **retinyl ester** and the specific flavonoid.

SUMM According to the present invention, by virtue of including an effective amount of naringenin or quercetin into compositions containing

retinol or a **retinyl ester**, the performance of the compositions is substantially improved. Alternatively, lower levels of **retinol** or a **retinyl ester** may be included in the composition containing naringenin or quercetin to equal the performance of a similar formulation without the. . .

DETD The inventive compositions contain, as a first essential ingredient, a compound selected from the group consisting of **retinol** and a **retinyl ester**.

DETD The term "**retinol**" includes the following isomers of **retinol**: all-trans-**retinol**, 13-cis-**retinol**, 11 -cis-**retinol**, 9-cis-**retinol**, 3,4-didehydro-**retinol**. Preferred isomers are all-trans-**retinol**, 13-cis-**retinol**, 3,4-didehydro-**retinol**, 9-cis-**retinol**. Most preferred is all-trans-**retinol**, due to its wide commercial availability.

DETD **Retinyl ester** is an ester of **retinol**. The term "**retinol**" has been defined above. **Retinyl esters** suitable for use in the present invention are C.sub.1 -C.sub.30 esters of **retinol**, preferably C.sub.2-C.sub.20 esters, and most preferably C.sub.2, C.sub.3, and C.sub.16 esters because they are more commonly available. Examples of **retinyl esters** include but are not limited to: retinyl palmitate, retinyl formate, retinyl acetate, retinyl propionate, retinyl butyrate, retinyl valerate, retinyl isovalerate,. . .

DETD The **retinoid** is employed in the inventive composition in an amount of from about 0.001% to about 10%, preferably in an amount. . .

DETD . . . for the active components in the composition, so as to facilitate their distribution when the composition is applied to the **skin**.

DETD Optional **Skin** Benefit Materials and Cosmetic Adjuncts

DETD . . . invention. Various types of active ingredients may be present in cosmetic compositions of the present invention. Actives are defined as **skin** or hair benefit agents other than emollients and other than ingredients that merely improve the physical characteristics of the composition.. . .

DETD Yet another preferred optional ingredient is selected from azoles, e.g., **climbazole**, bifonazole, clotrimazole, ketoconazole, miconazole, econazole, itraconazole, fluconazole, terconazole, butoconazole, sulconazole, lionazole and mixtures thereof.

DETD The composition according to the invention is intended primarily as a product for topical application to human **skin**, especially as an agent for conditioning and smoothening the **skin**, and preventing or reducing the appearance of wrinkled or aged **skin**.

DETD . . . a small quantity of the composition, for example from 1 to 5 ml, is applied to exposed areas of the **skin**, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the **skin** using the hand or fingers or a suitable device.

DETD The topical **skin** treatment composition of the invention can be formulated as a lotion, a fluid cream, a cream or a gel. The. . .

DETD **Retinoic acid** is more effective than **retinol** at altering keratinocyte differentiation state

DETD The effect on Transglutaminase levels normalized to DNA content of the cells after addition of **retinoic acid** and **retinol** was examined and the results are shown in Table 1.

Retinoids were obtained from Sigma.

DETD All concentrations of **retinoic acid** tested, i.e., 2.5.times.10.sup.-8 M, 2.5.times.10.sup.-8 M and 2.5.times.10.sup.-9 M decreased keratinocyte differentiation over both the ethanol control and did so to a significantly greater extent than each of the corresponding 2.5.times.10.sup.-7 M, 2.5.times.10.sup.-9 M and 2.5.times.10.sup.-9 M **retinol** treatments. The decrease in transglutaminase level was dose dependent for both **retinoic acid** and **retinol**. This is consistent with **retinoic acid** having a greater inhibitory effect on epithelial differentiation than **retinol**.

DETD Naringenin and **Retinol** Synergistically Inhibit Keratinocyte Differentiation

DETD TABLE 2

Effect of **Retinol** and Naringenin on Keratinocyle TGase/DNA

	mean TGase/ DNA .times. 10.sup.-5 .+-. s.d	p value vs p value. . . (100%)	p value vs
		--	0.235
			0.001
			0.329
2.5 .times. 10.sup.-7 M RA	22.47 .+-. 2.31 (42%)		
		0.001	
			0.001
		--	0.001
2.5 .times. 10.sup.-9 M **Retinol**	48.31 .+-. 5.31 (92%)		
		0.235	
		--	0.001
			0.585
10.sup.-7 M Naringenin	49.84 .+-. 2.76 (94%)		
		0.329	
		0.585	
			0.001
			--
2.5 .times. 10.sup.-9. . .			

DETD It can be seen from the results in Table 2 that 2.5.times.10.sup.-7 M **retinoic acid** was very effective at repressing keratinocyte TG1 levels (to 42%) of control level. 2.5.times.10.sup.-9 M **retinol** was ineffective (91%) and 10.sup.-7 M naringenin had no inhibitory effect on the keratinocyte TG1 level when used alone. However, 2.5.times.10.sup.-9 M **retinol** +10.sup.-9 M aringenin repressed keratinocyte TG1 to 53% of control levels. Naringenin and **retinol** therefore acted synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid.**

DETD It can be seen from the results in Table 3 that 2.5.times.10.sup.-7 M **retinoic acid** was very effective at repressing keratinocyte TG1 levels (to 32%) of control level. 2.5.times.10.sup.-8 M retinyl palmirate was ineffective (93%). . . and 10.sup.-8 M naringenin had a small inhibitory effect on the keratinocyte TG1 level when used alone. However 2.5.times.10.sup.-8 M **retinol** +10.sup.-8 M naringenin repressed keratinocyte TG1 to 85% of control

levels. Naringenin and retinyl palmitate therefore act synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid**.

DETD Quercetin and **Retinol** Synergistically Inhibit Keratinocyte Differentiation

DETD . . . (100%)

-- 0.042

0.001

0.001

2.5 .times. 10.sup.-7 M RA

35.91 .+-. 3.01 (52%)

0.001

0.001

-- 0.001

2.5 .times. 10.sup.-7 M **Retinol**

61.93 .+-. 5.18 (90%)

0.042

-- 0.001

0.328

10.sup.-6 M Quercetin

59.04 .+-. 3.38 (85%)

0.003

0.328

0.001

--

2.5 .times. 10.sup.-7. . .

DETD It can be seen from the results in Table 4 that 2.5.times.10.sup.-7 M **retinoic acid** was effective at repressing keratinocyte TG1 levels (to 52%) of control level. 2.5.times.10.sup.-7 M **retinol** was ineffective (90%) and 10.sup.-6 M quercetin had only a small inhibitory effect on the keratinocyte TG1 level when used alone.

However, 2.5.times.10.sup.-7 M **retinol** +10.sup.-6 M quercetin repressed keratinocyte TG1 to 70% of control levels. Quercetin and **retinol** therefore acted synergistically to repress keratinocyte differentiation in an analogous manner to the effect of **retinoic acid**.

DETD During the course of these studies, **retinoic acid** was used as positive control and reference compound against which the other compounds under analysis were compared. **Retinoic acid**, in a dose dependant manner decreased transglutaminase I levels in **skin** keratinocytes. In other words, **retinoic acid** decreased keratinocyte differentiation. **Retinol** and retinyl palmitate were significantly less effective than **retinoic acid** at inhibiting keratinocyte differentiation.

DETD The unexpected result demonstrated by Examples 2-4 however was that the effect of **retinol** and retinyl palmitate on cultured keratinocytes can be enhanced to levels approaching those of **retinoic acid** by combining **retinol** with a flavonoid such as naringenin or quercetin. This effect was not only greater than the effect of either **retinol** or the flavonoid itself but the two ingredients acted in synergy with each other to promote a **retinoic acid**-type response on the keratinocytes.

DETD The results documented above demonstrate that naringenin and/or quercetin act synergistically with **retinol** and **retinyl esters** to decrease keratinocyte differentiation, mimicking the effect of **retinoic acid**.

DETD ---

	% w/w
Retinol	0.5
Fully hydrogenated coconut oil	3.9
Naringenin	5
Brij 92*	5
Bentone 38	0.5
MgSO.sub.4 7H.sub.2 O	0.3
Butylated hydroxy toluene	0.01
Perfume	qs
Water	to 100

*Brij. . .
DETD

	% w/w
Retinoic acid	0.15
Mineral oil	4
Quercetin	1
Brij 56*	4
Alfol 16RD*	4
Triethanolamine	0.75
Butane-1,3-diol	3
Xanthan gum	0.3
Perfume	qs
Butylated hydroxy toluene	0.01
Water	to 100

*Brij 56. . .
DETD

	% w/w
Retinol	0.15
Naringenin	0.1
Ethanol 40	
Antioxidant	0.1
Perfume	qs
Water	to 100

DETD

	% w/w
Retinol	0.01
Quercetin	0.1
Silicone oil 200 cts	7.5
Glycerylmonostearate	3
Cetosteryl alcohol	1.6
Polyoxyethylene-(20)-cetyl alcohol	1.4
Xanthan gum	0.5
Parsol 1789	1.5
Octyl methoxycinnate (PARSOL MCX)	7
Perfume	qs

Color. . .
DETD This example illustrates a non-aqueous **skin** care composition incorporating the inventive combination.
DETD

	% w/w
Retinoic acid	0.15
Quercetin	1
Silicone gum SE-30.sup.1	10
Silicone fluid 345.sup.2	20
Silicone fluid 344.sup.3	55.79
Squalene	10
Linoleic acid	0.01
Cholesterol	0.03
2-hydroxy-n-octanoic acid	0.7
Herbal oil	0.5
Ethanol	2

. . .
CLM What is claimed is:
1. A **skin** conditioning composition comprising (a) from about 0.001% to about 10% of a compound selected from the group consisting of **retinol**, a **retinyl ester** and mixtures thereof; (b) from about 0.0001% to about 50% of a flavonoid selected from the group consisting of naringenin,. . .
2. The composition of claim 1 wherein the **retinyl ester** is selected from the group consisting of retinyl palmitate, retinyl acetate, retinyl propionate, retinyl linoleate and mixtures thereof.

3. The composition of claim 1 wherein ingredient (a) is **retinol** .

4. The composition of claim 1 wherein ingredient (a) is a **retinyl ester**.

5. A method of conditioning **skin** the method comprising applying topically to **skin** the composition of claim 1.

6. The method of treating **skin** conditions selected from the group consisting of dry **skin**, photodamaged **skin**, appearance of wrinkles, age spots, aged **skin**, acne, **skin** lightening, psoriasis, atopic dermatosis, and sebum secretion by applying to the **skin** a composition comprising: (a) from about 0.001% to about 10% of a compound selected from the group consisting of **retinol**, a **retinyl ester** and mixtures thereof; (b) from about 0.0001% to about 50% of a flavonoid selected from the group consisting of naringenin,. . .

L10 ANSWER 7 OF 8 USPATFULL
AB The present invention relates to a topical acne cream having primary ingredients such as: clortrimazole being an anti-fungal ingredient usually termed fungicidal due to its characteristic of killing fungus when they come in contact with the substance; betamethasone dipropionate

being an anti-inflammatory ingredient; and salicylic acid being an anti-septic/anti-bacterial/keratolytic substance which rapidly reduces inflammation caused by a person's body's immune reaction to acne bacteria as well as optional secondary ingredients such as binders, emulsifiers and fillers which may be present individually and in combination.

AN 96:29282 USPATFULL
TI Topical treatment for acne
IN Benitez, Juan E., 911 S. Airport Dr., Weslaco, TX, United States 78596
PI US 5505949 19960409 <--
AI US 1994-322691 19941013 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Venkat, Jyothsna
LREP Kroll, Michael I.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN 2 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1039
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5505949 19960409 <--

SUMM The present invention relates to the field of treating the **skin** condition known as acne. More specifically, the present invention is concerned with the prophylactic or therapeutic topical treatment of acne. Even more specifically, the present invention is concerned with the topical treatment of such **skin** disorders as acne vulgaris, other acneiform **dermal** disorders, e.g. preadolescent acne, acne rosacea (now known as rosacea), premenstrual acne, acne venenata, acne cosmetica, pomade acne, acne detergicans,. . . acne conglobata, or nodulocystic acne. The present invention can also be used for topically treating certain other types of acneiform **dermal** disorders, e.g. perioral dermatitis, seborrheic dermatitis in the presence of acne, gram negative folliculitis, sebaceous gland dysfunction, hiddradenitis suppurativa, pseudo-folliculitis. . .

SUMM . . . or thirties or may persist in adults for many years. Acne vulgaris most commonly occurs on oily areas of the **skin** with high sebaceous gland concentration. The areas of high sebaceous gland concentration are the face, ears, retroauricular areas (e.g. behind. . .

SUMM . . . eruptions can occur wherever there is a pilosebaceous unit or sebaceous follicle which does include the entire surface of the **skin**. The basic lesion in acne is the comedo commonly known as the blackhead. The comedo is created by retention of layers of dead **skin** known as keratin in the lining of the follicles. In addition to hyperkeratosis (which is thickening or retentative layering of. . .

SUMM Acne vulgaris can appear in many clinical varieties. The mildest case manifests comedones on oily **skin** and is called acne comedo.

SUMM This form of ache is common in adolescent **skin**, but it can be seen in all ages. The papular inflammatory form of acne can progress to an indurated, deeper,. . .

SUMM . . . acne which is manipulated or picked and causes further inflammation, more papules, and sometimes scars, pitting, and atrophy of the **skin**.

SUMM . . . mechanism is thought to be an inflammatory response to the end of hair (usually curly beard facial hair) into the **skin** causing a foreign body inflammatory response.

SUMM Hiddradenitis suppurativa is a suppurative (chronic) and cystic disease of apocrine gland regions of the **skin**, including the axillae,

perineum and groin.

SUMM . . . specifically, there is evidence for increased peripheral metabolic conversion of the androgen testosterone to dihydrotestosterone at the level of the **skin** in acne patients. It is further hypothesized that receptors on the sebaceous gland for the active androgen dihydrotestosterone can exhibit. . .

SUMM . . . present in abundance in pathologically affected sites. They are reduced during oral antimicrobial treatment, and their absence from nonhuman animal **skin** is striking especially since animals do not exhibit acne vulgaris.

SUMM Yet another causative factor in acne is the inflammatory response manifested in the **skin**. More specifically, it is thought that Proprionibacterium acnes lives in symbiosis on the keratin lined follicular canal. Proprionibacterium acnes ingests. . .

SUMM . . . lines 16-26, the bridged hyaluronic acid/cyanogen bromide/ampicillin conjugate, having been incorporated in a conventional medium, is applied directly to the **skin** to treat acne vulgaris. What may be risky about using this bridged hyaluronic acid/cyanogen bromide/ampicillin conjugate is that a quantity. . . after several rinses with absolute alcohol. Then, by applying some of this bridged hyaluronic acid/cyanogen bromide/ampicillin conjugate directly to the **skin** of patients, one may then be applying a residue of cyanogen bromide directly to the **skin** of patients.

SUMM . . . herein in the specification and claims is the acronym for Live Yeast Cell Derivative. The material is also known as **Skin** Respiratory Factor (SRF), Tissue Respiratory Factor (TRF), and Procytoxoid (PCO). The product, LYCD, is an alcoholic extract of viable Saccharomyces. . . 5 units to 40 units/mg of respiratory activity. In topical medicinal preparations it is characterized and quantified in terms of **Skin** Respiratory Factor (SRF) units. A unit of activity is calculated as the amount of SRF which is required to increase the oxygen uptake of 1 mg of dry weight rat abdominal **skin** by 1 percent at the end of a 1 hour testing period in a Warburg apparatus.

SUMM LYCD is also available as LYCODERM.RTM. ointment containing 2,000 units **Skin** Respiratory Factor (SRF) per ounce, from Arel Pharmaceuticals, Inc., Cincinnati, Ohio. In the prior art the well know hemorrhoidal ointment,. . . ounce of ointment. J. Z. Kaplan (Arch. Surge. 119(9) p. 1005-8 (1984) has reported that, in a double blind human **skin** graft study donor sites treated with LYCD ointment, statistically significant earlier angiogenesis and epitheliazation occurred as compared with donor sites. . .

SUMM . . . Cutis 17, 85-590 (1976), there is a substantial increase in the therapeutic effect when benzoylperoxide is used in combination with **retinoic acid**. Considerable disadvantages of such compositions are, however, that they frequently cause allergic contact dermatitis and/or that they are, in certain. . .

SUMM . . . the treatment of acne. Moreover, as a general rule, it is desirable to avoid oral therapy in the treatment of **skin** diseases whenever an effective topical treatment modality is available. Compositions, which are suitable for topical administration and which comprise benzoylperoxide. . .

SUMM . . . Although a positive effect was noted it was found that the numbers of Propionibacterium acnes and Staphylococcus epidermidis on the

skin were not altered, despite the in vitro activity of micronazole against Propionibacterium acnes.

SUMM 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethyl butan-2-one, generically designated as **climbazole**;

SUMM . . . activities on an examplitory bacterium such as Staphylococcus epidermidis, and Propionibacterium acnes, which microorganisms may all be recovered from the **skin**-lesions caused by acne vulgaris.

SUMM A method and composition for topically treating acne and acneiform **dermal** disorders includes applying an amount of an antibiotic selected from the group consisting of ampicillin, amoxicillin, other aminopenicillins, and cephalosporin, and derivatives and analogs thereof, effective to treat the acne and acneiform **dermal** disorders. The antibiotic is blended with a carrier suitable for topical application to **dermal** tissues. The carrier is selected from the group consisting of an aqueous liquid, an alcohol base, a water soluble gel,. . .

SUMM . . . applicant has, surprisingly, discovered that particularly effective, stable compositions can be obtained for treatment of acne, cutaneous ulcers, warts and **skin** dyskeratinization, also for the general treatment of dermatoses and cutaneous disorders, wherein clotrimazole, betamethasone dipropionate and salicylic acid may be. . .

SUMM . . . the invention are suitable for treatment of cutaneous disorders and dermatoses, such as acne in particular, cutaneous ulcers, warts and **skin** dyskeratinization.

SUMM . . . present invention to provide topically applied pharmaceutical compositions suitable for the treatment of various ailments and physical conditions of the **skin** such as acne, bed sores, burns, infections, trauma, ulcers, wounds, and wrinkles.

SUMM Accordingly, it is an object of the invention to provide a new topical treatment for acne and acneiform **dermal** disorders.

SUMM . . . will avoid the undesirable side effects of the currently available oral antibiotics for the systemic treatment of acne and acneiform **dermal** disorders, such as diarrhea, abdominal cramping, nausea, vomiting, drug eruptions, photosensitivity, blood dyscrasia (e.g. depression of white blood cell count. . .

SUMM . . . with clotrimazole, betamethasone dipropionate and salicylic acid may be combined with binders, fillers, and emulsifiers and applied topically to the **skin** of a patient suffering from acne and other acneiform **dermal** disorders.

SUMM . . . with clotrimazole, betamethasone dipropionate and salicylic acid may be combined with binders, fillers, and emulsifiers and applied topically to the **skin** of a patient suffering from acne and other acneiform **dermal** disorders. Suitable cephalosporins include cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephradine, cefaclor, cefamandole, cefonicid, ceforanide, cefotetan (a cephamycin), cefoxitin (a cephamycin),. . .

SUMM In a first treatment regimen, topical compositions of the invention are used alone to treat the acne and acneiform **dermal** disorders. In this respect, the topical compositions of the invention can be used as a first line treatment for acne and acneiform **dermal** disorders.

SUMM In this respect, after a conventional regimen of treating a patient for acne or acneiform **dermal** disorders with an orally administered antibiotic, such as tetracycline, minocycline, doxycycline, erythromycin, wherein the patient develops resistance or no improvement,. . .

SUMM . . . peroxide and/or topical tretinoin and/or any other topical agent currently used by physicians in the treatment of acne and acneiform **dermal** disorders.

SUMM . . . theoretical explanation as to why the compositions and the methods of the invention are efficacious in treating acne and acneiform **dermal** disorders, presentation of certain theoretical concepts may be of value.

SUMM . . . emulsifiers qualities of the compositions employed and the fact that a portion of the topically applied is absorbed by the **skin** and enters the patient's bloodstream.

DETD . . . acid 22. When the topical acne cream 10 is applied to active acne 16B, the primary ingredients absorb into the **skin** through spaces between the cells as well as into the sebaceous glands and hair follicles, thus, permitting the active ingredients. . .

L10 ANSWER 8 OF 8 USPATFULL

AB Novel compositions for the topical treatment of acne vulgaris said compositions comprising a pharmaceutically acceptable amount of benzoylperoxide and an anti-microbially effective amount of a suitable azole derivative.

AN 84:24461 USPATFULL

TI Anti-microbial compositions for the topical treatment of acne vulgaris

IN Van Bever, Willem F. M., Turnhout, Belgium

PA Janssen Pharmaceutica N.V., Beerse, Belgium (non-U.S. corporation)

PI US 4446145 19840501 <--

AI US 1981-282975 19810713 (6)

RLI Continuation-in-part of Ser. No. US 1980-114813, filed on 24 Jan 1980, now abandoned

DT Utility

FS Granted

EXNAM Primary Examiner: Schenkman, Leonard

LREP Dellenbaugh, Geoffrey G.

CLMN Number of Claims: 4

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 559

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 4446145 19840501 <--

SUMM . . . Cutis 17, 585-590 (1976), there is a substantial increase in the therapeutic effect when benzoylperoxide is used in combination with **retinoic acid**. Considerable disadvantages of such compositions are, however, that they frequently cause allergic contact dermatitis and/or that they are, in certain. . .

SUMM . . . the treatment of acne. Moreover, as a general rule, it is desirable to avoid oral therapy in the treatment of **skin** diseases whenever an effective topical treatment modality is available. Compositions, which are suitable for topical administration and which comprise benzoylperoxide. . .

SUMM . . . Although a positive effect was noted it was found that the numbers of Propionibacterium acnes and Staphylococcus epidermidis on the **skin** were not altered, despite the in vitro activity of micronazole against Propionibacterium acnes.

SUMM 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethylbutan-2-one, generically designated as **climbazole**;

SUMM . . . epidermidis B 2689 and B 180, and Propionibacterium acnes B 22, 267, which microorganisms may all be recovered from the **skin** -lesions caused by acne vulgaris.

SUMM . . . acne grading scale. Furthermore, comedones were counted and patients were questioned about side-effects such as, for example, irritation of the **skin**.

SUMM . . . azole derivative are administered separately. This mutually potentiating activity results in a decrease of the number of comedones in the **skin** of patients suffering from acne vulgaris when treated with a composition comprising benzoylperoxide and an azole derivative of formula (I),. . .

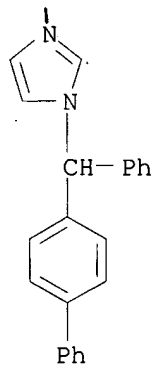
SUMM . . . compositions have the advantage that comparable and even higher activities are obtained at lower concentrations of benzoylperoxide, thus avoiding undesirable **skin** irritations while simultaneously effectively treating the acne.

SUMM . . . preferably be non-irritating and as far as possible they should be odorless and non-toxic. For convenience in applying to the **skin**, the compositions usually contain, besides from about 40 to about 90% of water or an organic solvent, several of certain. . .

=>

```
> s sphingomyelin/cn
L1            1 SPHINGOMYELIN/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   85187-10-6  REGISTRY *
* Use of this CAS Registry Number alone as a search term in other STN files
may
  result in incomplete search results.  For additional information, enter HELP
  RN* at an online arrow prompt (=>).
CN   Sphingomyelins  (CA INDEX NAME)
OTHER NAMES:
CN   Ceramides, 1-(dihydrogen phosphates), monoesters with choline hydroxide,
     inner salts
CN   Phosphatides, sphingosine-contg.
CN   Phosphingosides
CN   Phospholipids, sphingomyelins
CN   Sphingolipids, sphingomyelins
CN   Sphingomyelin
MF   Unspecified
CI   MAN, CTS
SR   Commission of European Communities
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CHEMCATS,
       CHEMLIST, CIN, CSCHEM, EMBASE, IFICDB, IFIUDB, IPA, MEDLINE, NAPRALERT,
       TOXCENTER
     Other Sources:   EINECS**
         (**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***


=> s bifonazole/cn
L2            1 BIFONAZOLE/CN

=> d

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   60628-96-8  REGISTRY
CN   1H-Imidazole, 1-([1,1'-biphenyl]-4-ylphenylmethyl)- (9CI)  (CA INDEX
NAME)
OTHER NAMES:
CN   (.+-.)-Bifonazole
CN   BAY-h 4502
CN   Bifazol
CN   Bifonazole
CN   Mycospor
CN   Trifonazole
DR   162824-44-4
MF   C22 H18 N2
CI   COM
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS,
BIOSIS,
       BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST,
       CIN, DDFU, DRUGPAT, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA,
MEDLINE,
       MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN,
       USPAT2, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   EINECS**, WHO
```

(**Enter CHEMLIST File for up-to-date regulatory information)



514 / 385

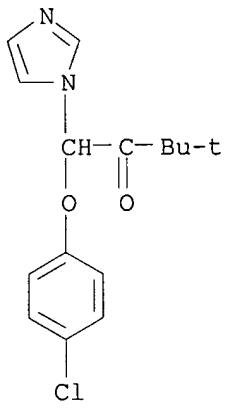
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

293 REFERENCES IN FILE CA (1962 TO DATE)
7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
294 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> s climbazole/cn
L3 1 CLIMBAZOLE/CN

=> d

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 38083-17-9 REGISTRY
CN 2-Butanone, 1-(4-chlorophenoxy)-1-(1H-imidazol-1-yl)-3,3-dimethyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1-[(4-Chlorophenoxy)(tert-butylcarbonyl)methyl]imidazole
CN BAY-e 6975
CN Baypival
CN **Climbazole**
CN Crinipan AD
FS 3D CONCORD
DR 75536-35-5
MF C15 H17 Cl N2 O2
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CSCHEM, DDFU, DRUGPAT, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MSDS-OHS, PROMT, RTECS*, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

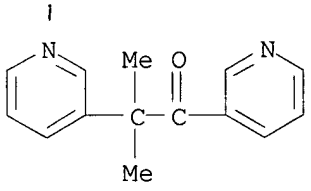
99 REFERENCES IN FILE CA (1962 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
99 REFERENCES IN FILE CAPLUS (1962 TO DATE)

=> s metyrapone/cn
L4 1 METYRAPONE/CN

=> d

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 54-36-4 REGISTRY
CN 1-Propanone, 2-methyl-1,2-di-3-pyridinyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Propanone, 2-methyl-1,2-di-3-pyridyl- (6CI, 8CI)
OTHER NAMES:
CN 1,2-Bis(3-pyridyl)-2-methyl-1-propanone
CN 2-Methyl-1,2-bis(3-pyridyl)-1-propanone
CN 2-Methyl-1,2-di(.beta.-pyridyl)-1-propanone
CN 2-Methyl-1,2-di-3-pyridyl-1-propanone
CN Mepyrapone
CN Methapyrapone
CN Methopirapone
CN Methopyrapone
CN Methopyrinine
CN Methopyrone
CN Metopiron
CN Metopirone
CN Metopyrone
CN Metyrapon
CN **Metyrapone**
CN Su 4885
FS 3D CONCORD
DR 37245-80-0
MF C14 H14 N2 O
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IPA, MEDLINE, MRCK*, NIOSHTIC, PROMT, RTECS*, SPECINFO,

TOXCENTER, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



514/332

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1470 REFERENCES IN FILE CA (1962 TO DATE)
28 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1472 REFERENCES IN FILE CAPLUS (1962 TO DATE)
145 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

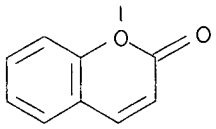
=> coumarin/cn
COUMARIN IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s coumarin/cn
L5 1 COUMARIN/CN

=> d

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 91-64-5 REGISTRY
CN 2H-1-Benzopyran-2-one (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **Coumarin (8CI)**
OTHER NAMES:
CN 1,2-Benzopyrone
CN 2-Propenoic acid, 3-(2-hydroxyphenyl)-, .delta.-lactone
CN 5,6-Benzo-2-pyrone
CN Benzo-.alpha.-pyrone
CN cis-o-Coumarinic acid lactone
CN Coumarinic anhydride
CN o-Hydroxycinnamic acid lactone
CN Rattex
CN Tonka bean camphor
FS 3D CONCORD
MF C9 H6 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS,
BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB,
CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,
DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB,
IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC,
PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, ULIDAT, USAN,
USPAT2,
USPATFULL

(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



514/460

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5350 REFERENCES IN FILE CA (1962 TO DATE)
1384 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5362 REFERENCES IN FILE CAPLUS (1962 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>